Neuroscience Education Institute

ON THE BLUE END: DIAGNOSIS AND TREATMENT OF BIPOLAR DEPRESSION

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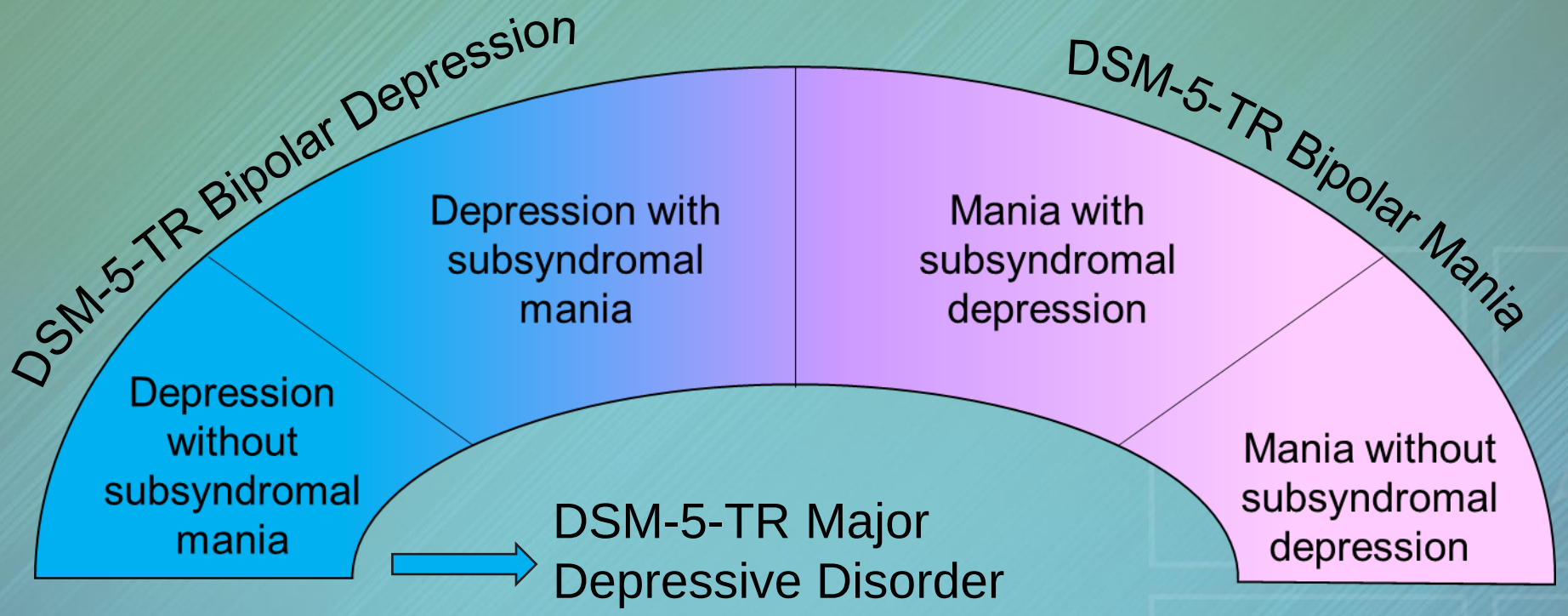
Learning Objectives

- Identify factors that contribute to the misdiagnosis of bipolar depression
- Recognize the clinical presentation of bipolar depression in pediatric and adult patients
- Implement appropriate tools to assess patients with depression for signs of bipolarity
- Utilize evidence-based strategies to improve treatment of bipolar depression in patients of all ages

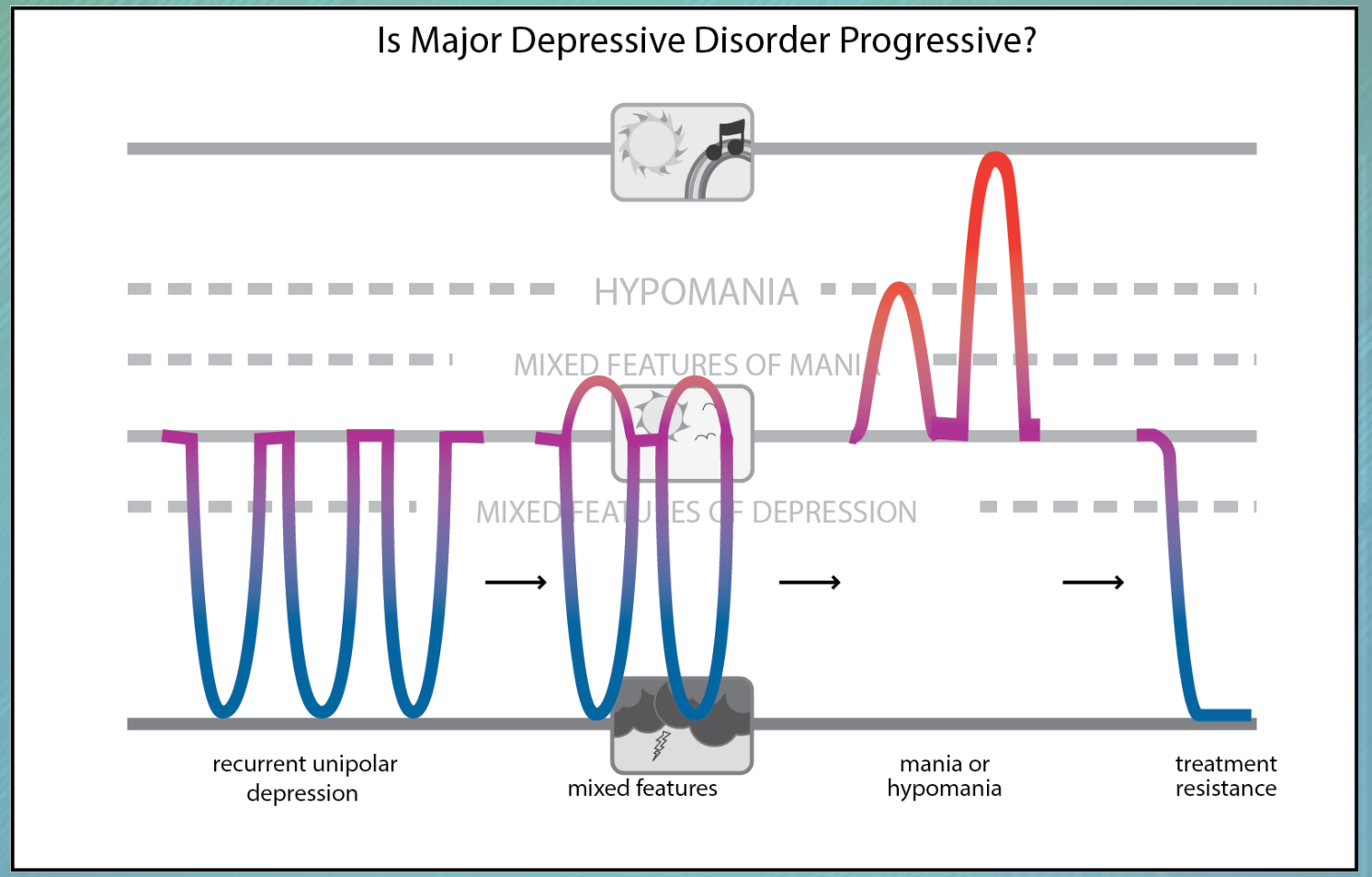
The Mood Disorder Spectrum



- Although categorical classifications may be useful for clinical practice, the overwhelming majority of the evidence points to a dimensional (spectrum) view of mood disorders
  - e.g., treatment response (antidepressant vs. mood stabilizing agent) and links with family history of bipolar disorder

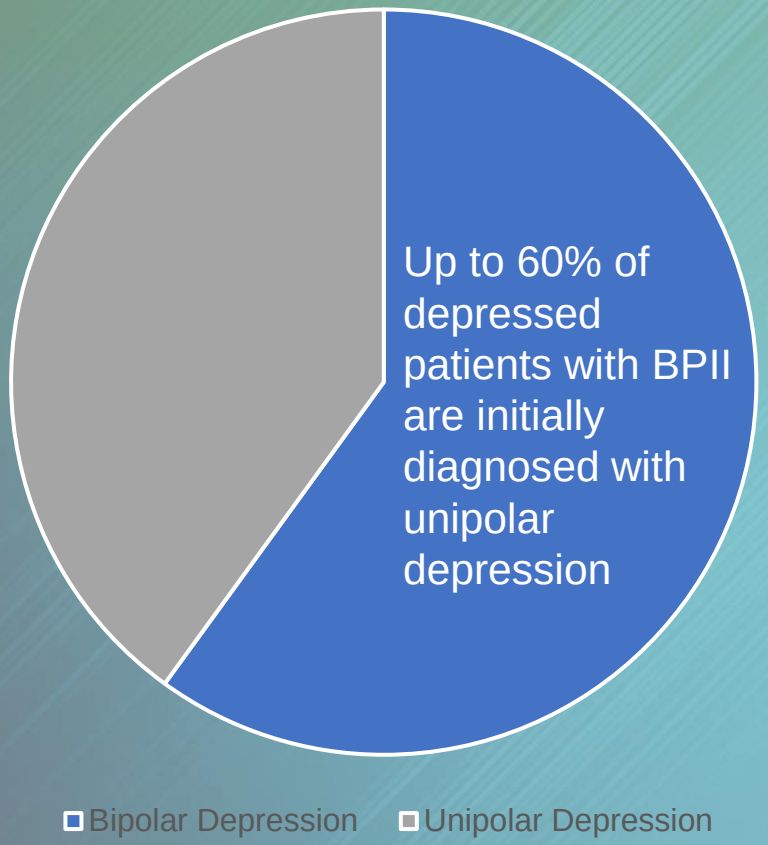
Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

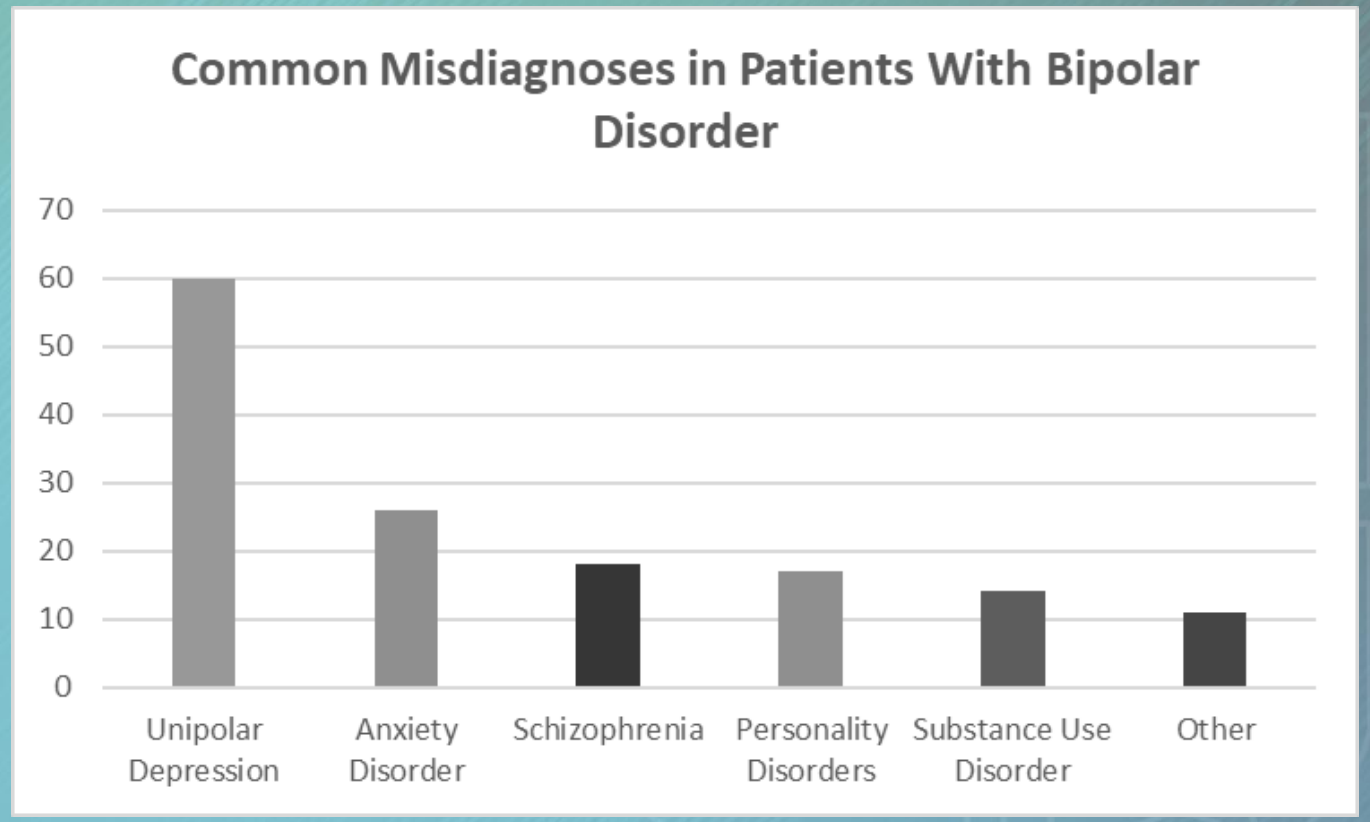
Can Unipolar Depression Convert to Bipolar Depression?



Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021; Fiedorowicz JG et al. Am J Psychiatry 2011;168(1):40-8; Van Meter A et al. J Affect Disord 2018;238:375-82.

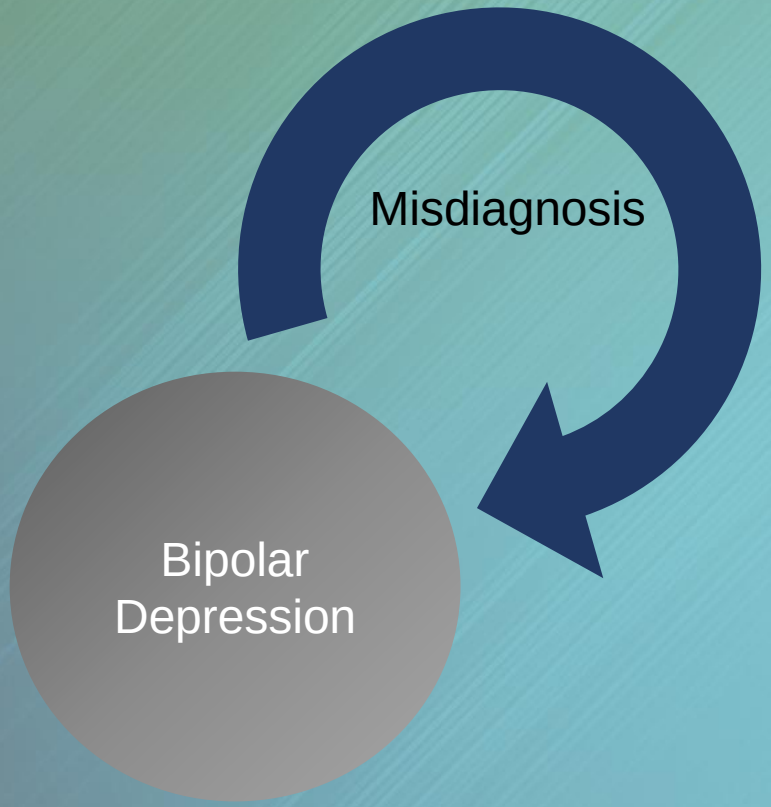
Misdiagnoses and Underdiagnoses Are Common Among Patients With Bipolar Disorder





Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021; Hirschfeld RM et al. J Clin Psychiatry 2003;64(2):161-74; Singh MK et al. Bipolar Disord 2021;23(8):834-7.

Factors That Contribute to Misdiagnosis



Reasons for misdiagnosis:

- Incomplete understanding of bipolar disorder by healthcare professionals
- Overlooked or no history of mania
- Failure to differentiate symptoms that can help identify unipolar and bipolar depression

Consequences of misdiagnosis:

- Inappropriate use of antidepressant agents
- Increased acute risk of switching from depression to mania/hypomania with antidepressant use
- Delay of proper treatment

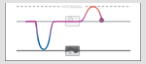
McIntyre RS et al. Curr Med Res Opin 2019;35(11):1993-2005.

Why Is Making an Early and Accurate Diagnosis of Bipolar Depression So Difficult?

- Hypomania is often pleasant for patients and may not be mentioned by them
- Mania is often atypical (especially in youth) with irritability and flight of ideas rather than euphoria and grandiosity
- Patients with bipolar depression (BD) typically seek help during depressive, not manic, episodes (mixed features may be present)
- Clinicians will first be confronted with differentiating between unipolar and bipolar depression

Conus P et al. Bipolar Disord 2014;16(5):548-56; Phillips ML, Kupfer DJ. Lancet 2013;381(9878):1663-71; Bobo WV. Mayo Clin Proc 2017;92(10):1532-51.

Why Is an Early, Accurate Diagnosis Important?

Consequences of not identifying bipolar depression (BD) early:	
Impaired quality of life	
Inaccurate and potentially harmful treatment	
Increased cycling and risk of relapse	
Increased risk of suicide	
Increased subsequent morbidity	
High economic costs	$ $ $
Overall mortality rate for BP is over 2.5X higher than the general population	

Conus P et al. Bipolar Disord 2014;16(5):548-56; Lomholt LH et al. Int J Bipolar Disord 2019;7(1):6; Youngstrom EA at al. 2008;10(1 Pt 2):194-214.

So You Think It's Unipolar Depression?

- Correct diagnosis of bipolar disorder (BP) within the first year of symptom onset is made in only 20% of cases
- Over 1/3 of unipolar patients are eventually re-diagnosed as bipolar
- Average time between onset of BP symptoms and first appropriate treatment = 10 years
- Presence of even subthreshold (hypo)mania symptoms is strongly associated with conversion to bipolar disorder
    - Each (hypo)mania symptom increases risk by ~30%

Akiskal HS, Benazzi F. J Affect Disord 2003;73(1-2):113-22; Dudek D et al. J Affect Disord 2013;144(1-2):112-5; Fiedorowicz JG et al. Am J Psychiatry 2011;168(1):40-8; Conus P et al. Bipolar Disord 2014;16(5):548-56; Kleine-Budde K et al. Bipolar Disord 2014;16(4):337-53; Knežević V, Nedić A. Eur Rev Med Pharmacol Sci 2013;17(11):1542-5; Phillips ML, Kupfer DJ. Lancet 2013;381(9878):1663-71; Sasdelli A et al. Psychiatry J 2013;2013:548349.

Symptoms With Potential Diagnostic Utility in Bipolar and Unipolar Depression: A Probabilistic Approach

Bipolar Depression

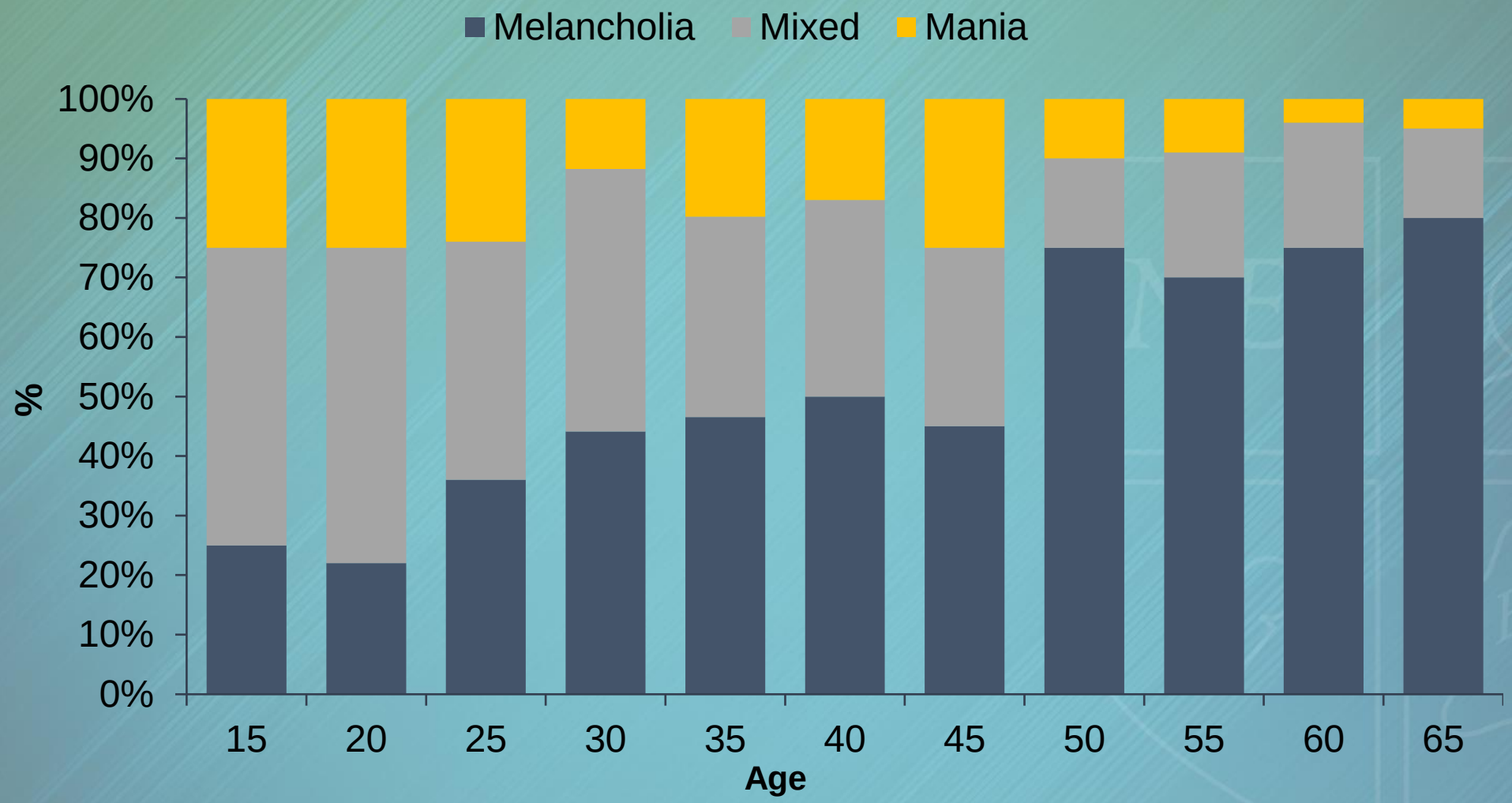
- Early onset of depression (<25 years)
- Multiple prior episodes (≥5)
- Positive family history of bipolar disorder
- Hypersomnia/increased daytime napping
- Hyperphagia/increased weight
- Atypical depression signs
- Psychomotor retardation
- Psychotic features/pathological guilt
- Mood lability/irritability/psychomotor agitation/racing thoughts
- Postpartum affective symptoms
- Substance abuse
- Anxiety disorders

Unipolar Depression

- Late onset of first depression (>25 years)
- Long duration of current episode (>6 months)
- Negative family history of bipolar depression
- Initial insomnia/reduced sleep
- Appetite/weight loss
- Normal or increased activity levels
- Somatic complaints
- Tendency to blame others
- Anxiety

McIntyre RS, Calabrese JR. Curr Med Res Opin 2019;5:1-13; McIntyre RS et al. Lancet 2020: S0140-6736(20)31544-0.

Mood State at Presentation Across the Life Cycle



N=889

Kraepelin E. Manic-depressive insanity and paranoia. Edinburgh: E&S Livingstone; 1921:169.

Presentation of Bipolar Depression in Youth

Bipolar Depression (BP) in Youth

- BP depression is more common than mania or hypomania in youth
- Irritability may occur without any accompanying elation or high mood
- Mixed episodes occur commonly
- Mixed presentations in youth with BP have been linked to increased suicide
- Youth with BP are more likely to relapse into depressive or mixed episodes than manic episodes

Cosgrove et al. Pediatr Drugs 2013;15:83-91.

Screening for Bipolar Depression

Mood Disorder Questionnaire (MDQ)

1. Has there ever been a period of time when you were not your usual self and...		
...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	◯	◯
...you were so irritable that you shouted at people or started fights or arguments?	◯	◯
...you felt much more self-confident than usual?	◯	◯
...you got much less sleep than usual and found you didn't really miss it?	◯	◯
...you were much more talkative or spoke faster than usual?	◯	◯
...thoughts raced through your head or you couldn't slow your mind down?	◯	◯
...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	◯	◯
...you had much more energy than usual?	◯	◯
...you were much more active or did many more things than usual?	◯	◯
...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	◯	◯
...you were much more interested in sex than usual?	◯	◯
...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	◯	◯
...spending money got you or your family in trouble?	◯	◯

2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time? *Please check 1 response only.*	◯	◯
3. How much of a problem did any of these cause you — like being able to work; having family, money, or legal troubles; getting into arguments or fights? *Please check 1 response only.* ◯ No problem ◯ Minor problem ◯ Moderate problem ◯ Serious problem		
4. Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?	◯	◯
5. Has a health professional ever told you that you have manic-depressive illness or bipolar disorder?	◯	◯

This questionnaire should be used as a starting point. It is not a substitute for a full medical evaluation. Bipolar disorder is a complex illness, and **an accurate, thorough diagnosis can only be made through a personal evaluation by your doctor.**

Adapted from Hirschfeld R, Williams J, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: the Mood Disorder Questionnaire. *Am J Psychiatry.* 2000;157:1873-1875.

This instrument is designed for screening purposes only and is not to be used as a diagnostic tool.

How to Use

The questionnaire takes less than 5 minutes to complete. Patients simply check the yes or no boxes in response to the questions. The last question pertains to the patient's level of functional impairment. The physician, nurse, or medical staff assistant then scores the completed questionnaire.

How to Score

Further medical assessment for bipolar disorder is clearly warranted if patient:

- Answers *Yes* to 7 or more of the events in question #1

AND

- Answers *Yes* to question #2

AND

- Answers *Moderate problem* or *Serious problem* to question #3

Rapid Mood Screener (RMS)

Download for free. DOI: 10.1080/03007995.2020.1860358

Item	Response	
1. Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?	Yes	No
2. Did you have problems with depression before the age of 18?	Yes	No
3. Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?	Yes	No
4. Have you ever had a period of at least 1 week during which you were more talkative than normal with thoughts racing in your head?	Yes	No
5. Have you ever had a period of at least 1 week during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic?	Yes	No
6. Have you ever had a period of at least 1 week during which you needed much less sleep than usual?	Yes	No

Highest estimated accuracy was observed with ≥4 "yes" responses

- RMS sensitivity was 0.88 and specificity was 0.80; concordance index 0.87
- MDQ sensitivity was 0.86 and specificity was 0.78; concordance index 0.82

McIntyre RS et al. Curr Med Res Opin 2021;37(1):135-44.

Screening for Signs of Bipolarity in Depression: Mania/ Hypomania

Family History

- Although the majority of patients with BD do not have a family history of BP, family history of BP is arguably the most robust and reliable risk factor for BD
- Individuals with a first-degree relative with BP are at an 8x greater risk of developing BP compared to the general population
- The importance of questioning depressed patients about family history of affective disorders can not be overemphasized

Duffy A et al. Br J Psychiatry 2014;204(2):122-8; Malhi GS et al. Bipolar Disord 2014;16(5):455-70; Perlis RH et al. Am J Psychiatry 2006; 163(2):225-31; Wilde A et al. J Affect Disord 2014;158:37-47; Birmaher B et al. Am J Psychiatry 2009;166(7):795-804.

Screening for Mixed Features

Manic or hypomanic episode, with mixed features
Full criteria for manic or hypomanic episode
At least three of the following symptoms of depression:
Depressed mood
Loss of interest or pleasure
Psychomotor retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive or inappropriate guilt
Recurrent thoughts of death or suicidal ideation/actions
Depressive episode, with mixed features
Full criteria for a major depressive episode
At least three of the following manic/hypomanic symptoms:
Elevated, expansive mood (e.g., feeling high, excited, or hyper)
Inflated self-esteem or grandiosity
More talkative than usual or feeling pressured to keep talking
Flight of ideas or subjective experience that thoughts are racing
Increase in energy or goal-directed activity
Increased or excessive involvement in activities that have a high potential for painful consequences
Decreased need for sleep
(*Not included: psychomotor agitation)
(*Not included: irritability)
(*Not included: distractibility)

Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

Detection of Subthreshold Hypomanic Symptoms

- Mood Disorder Questionnaire (MDQ)
- Rapid Mood Screener (RMS)
- Bipolar Depression Rating Scale (BDRS)
- Hypomania Interview Guide (HIG)
- Mini International Neuropsychiatric Interview (M.I.N.I.)
- Clinically Useful Depression Outcome Scale with DSM-5 Mixed (CUDOS-M)
- Hypomania Checklist (HCL-32)
- Altman Mania Rating Scale
- General Behavior Inventory (GBI)

Hirschfeld RM et al. Am J Psychiatry 2000;157(11):1873-5; Montano CM et al. NEI VPL 2020; Galvão F et al. Comp Psychiatry 2013;54(6):605-10; Williams JB et al. Depress Anxiety 1999;9(2):92-100; Benazzi F. Prog Neuropsychopharmacol Biol Psychiatry 2003;27(1):129-34; Hergueta T, Weiller E. Int J Bipolar Disord 2013;1:21; Zimmerman M et al. J Affect Disord 2014;168:357-62; Prieto ML et al. J Affect Disord 2015;172:355-60; Altinbas K et al. J Affect Disord 2014;152-154:478-82; Altman EG et al. Biol Psychiatry 1997;42(10):948-55; Stahl SM et al. CNS Spectr 2017;22(2):203-19; Youngstrom EA et al. J Clin Child Adolesc Psychol 2021;50(5):579-95.

The "Four A's" Increase Suspicion of Mixed Features

Mixed episode

- Described in the DSM-IV-TR
- Requires an individual to simultaneously meet the criteria for a major depressive episode and a manic episode

Mixed features specifier

- Described in the DSM-5
- Can be applied to episodes of major depression, mania, and hypomania
- Requires the presence of at least three manic or hypomanic non-overlapping symptoms during a major depressive episode
- Requires the presence of at least three depressive non-overlapping symptoms during a hypomanic or manic episode

DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, text revised
DSM-5=*Diagnostic and Statistical Manual of Mental Disorders*, 5th edition

Clinicians should be aware of "**the four A's**":

- Anxiety
- Agitation
- Anger/irritability
- Attentional disturbance-distractibility

These symptoms are highly suggestive of mixed features in individuals with mood disorders

McIntyre RS et al. Lancet 2020;396(10256):1841-56.

One of the Most Important Questions to Ask Any Patient With Depression

Any manic/hypomanic symptoms and/or family history of bipolar disorder?

Every patient. Every time.

Barbara Geller's Work in Pediatric Bipolar Disorder

- Geller B, et al. J Child Adolesc Psychopharmacol. 2002 Spring;12(1):3-9. This article talks about grandiosity, hypersexuality, etc in helping diagnose BPD vs ADHD.

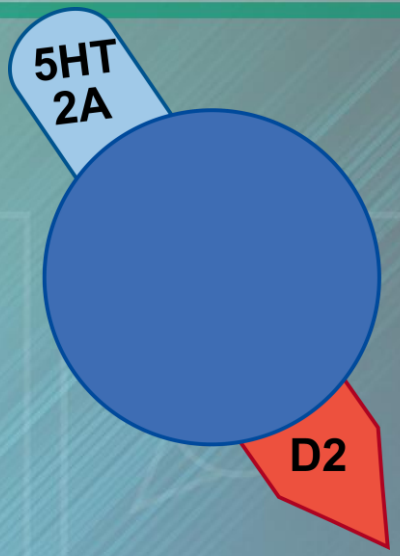
- Geller B, Fox LW, Clark KA (1994), Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children. J Am Acad Child Adolesc Psychiatry 33(4):461-468

- Geller B, Luby J (1997), Child and adolescent bipolar disorder: a review of the past 10 years. [Erratum appears J Am Acad Child Adolesc Psychiatry 1997; 36(11):1642.] J Am Acad Child Adolesc Psychiatry 36(9):1168-1176

- Geller, B., & DelBello, M. P. (Eds.). (2003). Bipolar disorder in childhood and early adolescence. The Guilford Press. This is a landmark book.

Treatments for Bipolar Depression

Serotonin/Dopamine Antagonists/Partial Agonists Across the Depression Spectrum



- There is a major paradigm shift away from monoamine reuptake inhibitors for depression with mixed features
- Serotonin/ dopamine antagonists/ partial agonists are effective at treating: bipolar depression and treatment-resistant depression (TRD)
- Several of the agents that are approved for bipolar depression are also effective for depression with mixed features
- There are currently no agents approved to treat mixed depression

Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

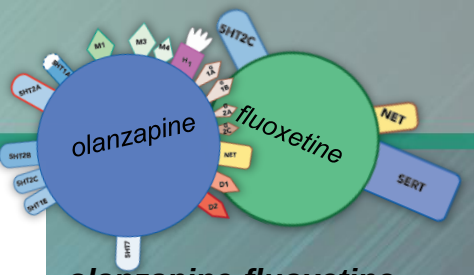
Atypical Antipsychotics

	Evidence of efficacy in mixed features	FDA-approved for BP depression	FDA-approved for BP mania	FDA-approved for BP maintenance	FDA-approved for MDD
Aripiprazole			☑	☑	☑ (adjunct)
Asenapine	☑ MMX		☑	☑	
Brexpiprazole					☑ (adjunct)
Cariprazine	☑MMX, DMX	☑	☑		
Lurasidone	☑ DMX	☑			
Olanzapine	☑ MMX	☑ (with fluoxetine)	☑	☑	☑ (with fluoxetine)
Quetiapine	☑ MMX	☑	☑	☑	☑ (adjunct)
Risperidone			☑	☑	
Ziprasidone	☑ MMX		☑	☑	
Lumateperone	☑ DMX	☑			

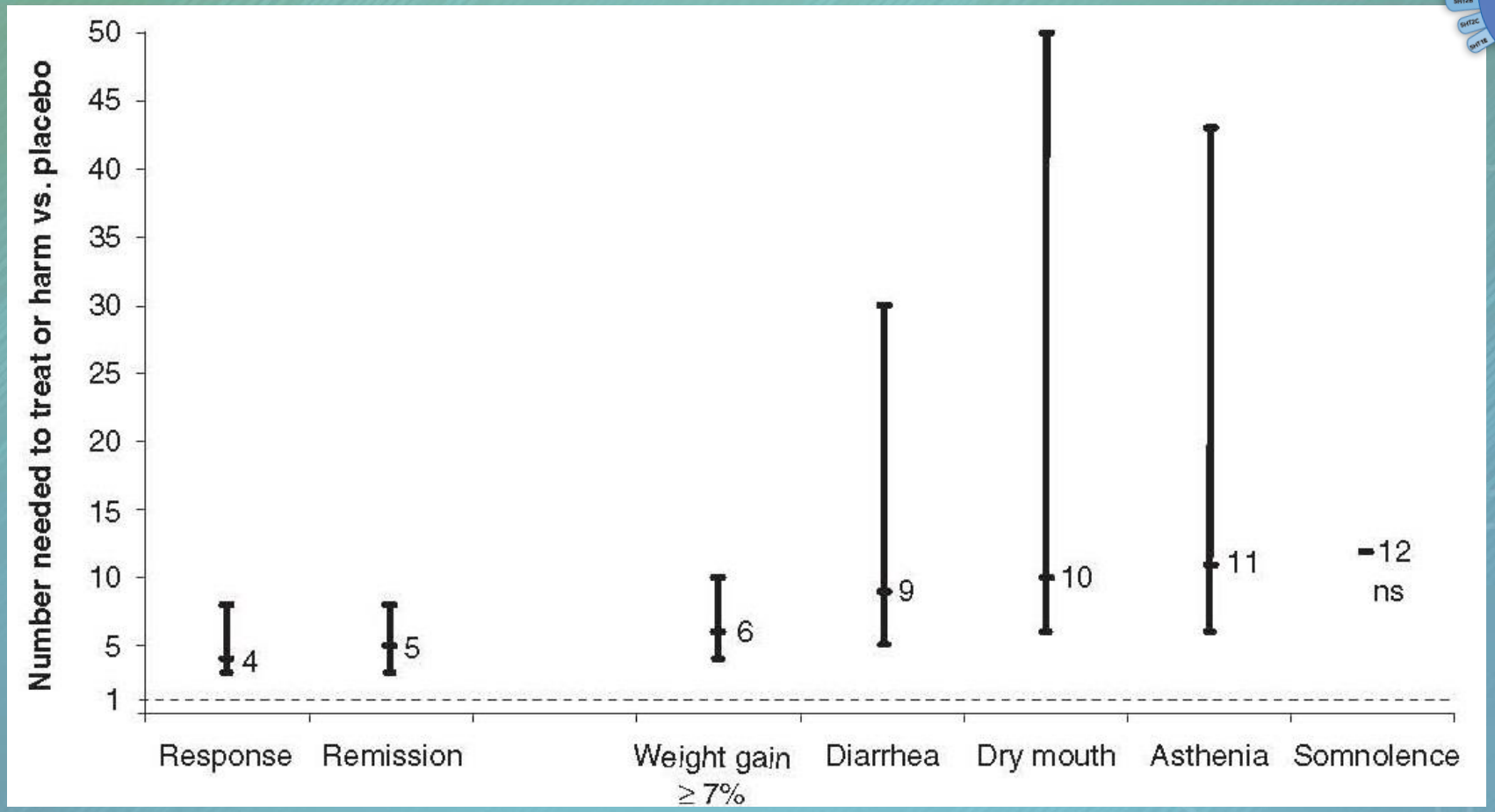
DMX: depressive mixed state;
MMX: mania with mixed features

Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

Olanzapine-Fluoxetine Combination (OFC) in Bipolar Depression



olanzapine-fluoxetine

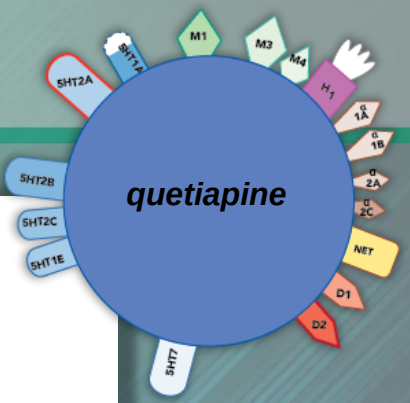


Data from two 8-week randomized clinical trials for bipolar depression. Primary measure was change in MADRS; OFC was significantly superior to both OLZ and PBO.

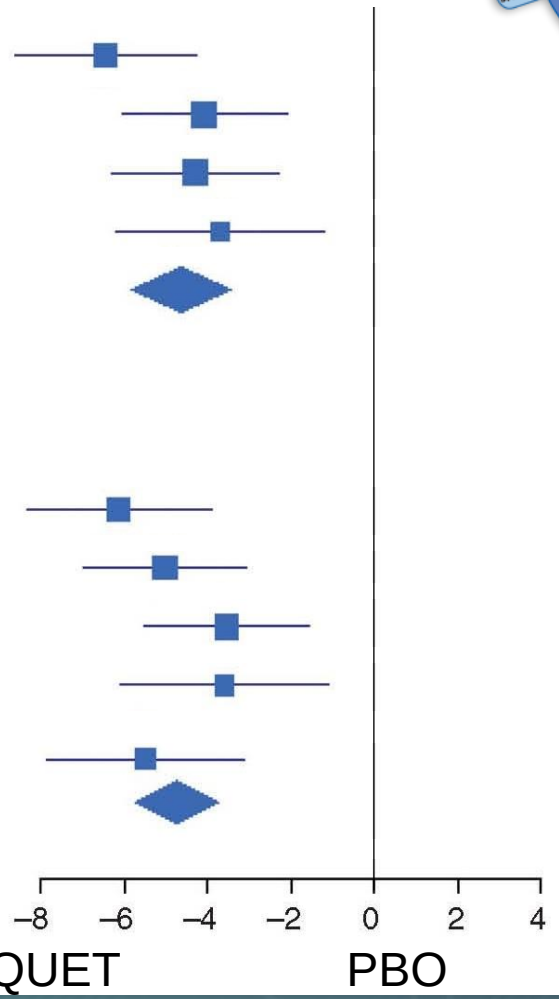
OFC: n=86, mean daily dose 7.4 mg/39.3 mg. OLZ: n=370, mean daily dose 9.7 mg. PBO: n=377.

Citrome L. Expert Opinion Pharmacother 2011;12(17):2751-8.

Quetiapine in Bipolar Depression

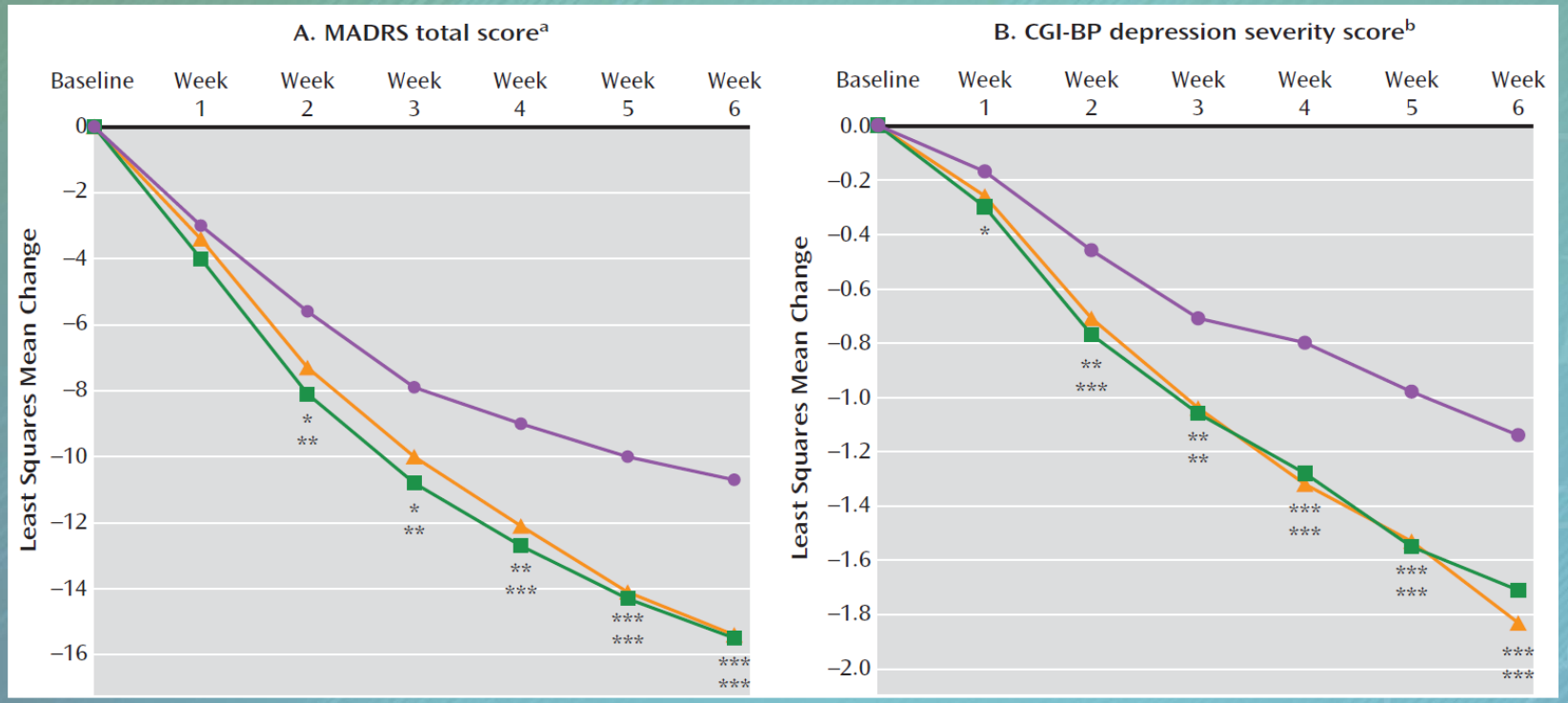


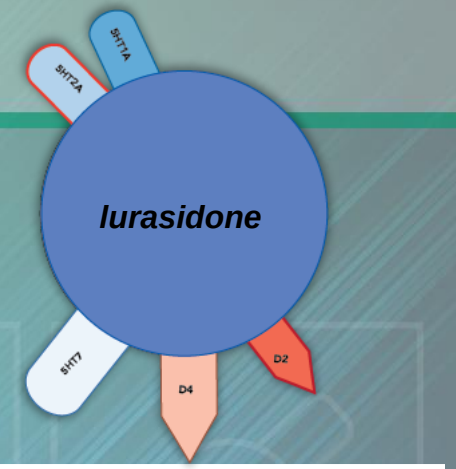
Study	MADRS WMD (95% CI)
Calabrese et al. 2005	-6.47 (-8.67; -4.27)
Thase et al. 2006	-4.07 (-6.03; -2.11)
Young et al. 2010	-4.29 (-6.28; -2.3)
McElroy et al. 2010	-3.71 (-6.22; -1.2)
Quetiapine 600 pooled	**-4.64 (-5.82; -3.46)**
Heterogeneity: Q=3.64; p=0.303	
Overall: Z=-7.71; p=0; n=1396	
Calabrese et al. 2005	-6.13 (-8.33; -3.93)
Thase et al. 2006	-5.01 (-6.95; -3.07)
Young et al. 2010	-3.55 (-5.55; -1.55)
McElroy et al. 2010	-3.59 (-6.1; -1.08)
Suppes et al. 2010	-5.51 (-7.88; -3.14)
Quetiapine 200 pooled	**-4.76 (-5.75; -3.76)**
Heterogeneity: Q=4.19; p=0.381	
Overall: Z=-9.37; p=0; n=1661	



Chiesa A et al. Int Clin Psychopharmacol 2012;27(2):76-90.

Lurasidone Monotherapy in the Treatment of Bipolar I Depression



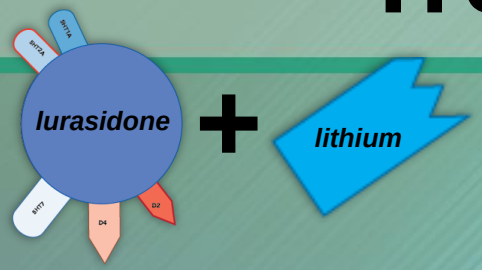


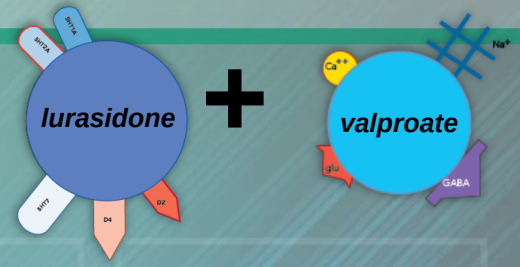
A randomized, double-blind, placebo-controlled study

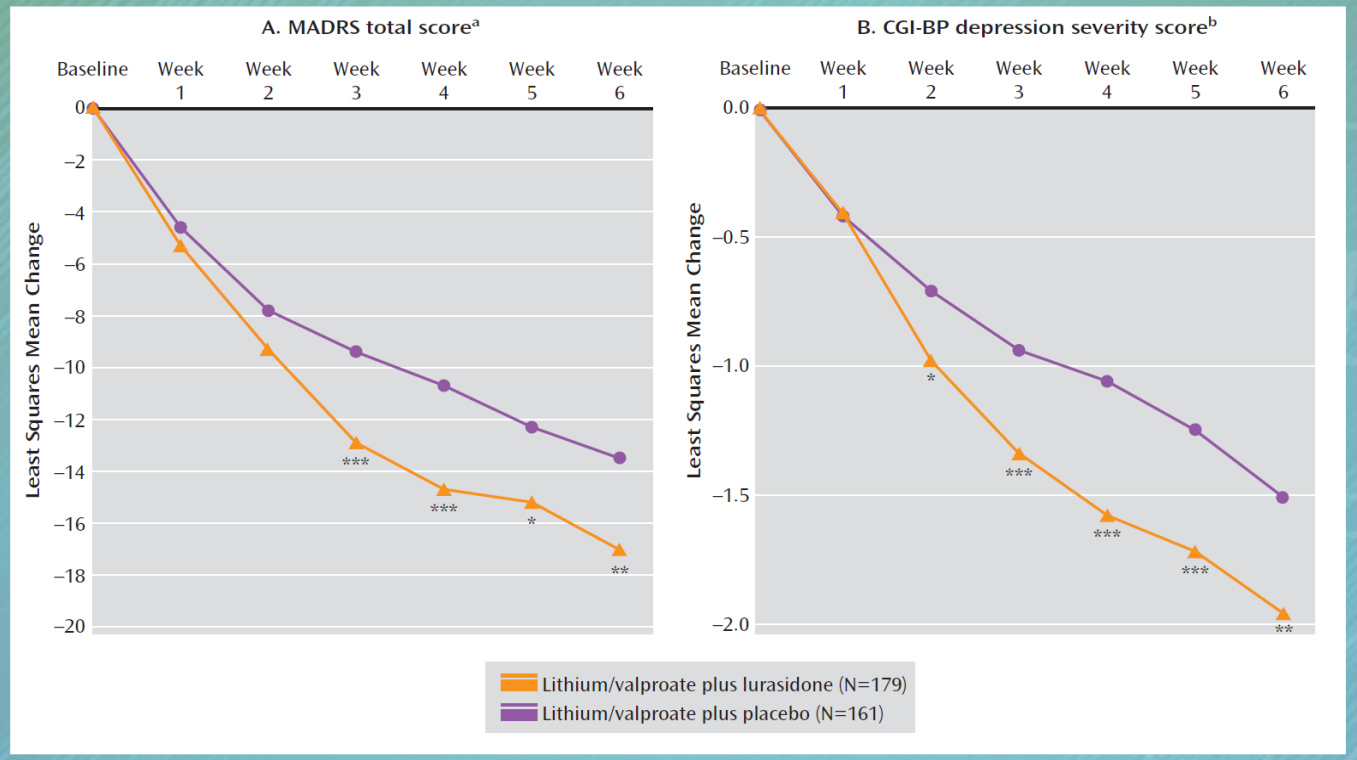
A. Mean scores at baseline were 30.3 (SD=5.0), 30.6 (SD=4.9), and 30.5 (SD=5.0) for the lurasidone 20–60 mg, lurasidone 80–120 mg, and placebo groups, respectively.
B. Mean scores at baseline were 4.52 (SD=0.62), 4.55 (SD=0.64), and 4.48 (SD=0.61) for the lurasidone 20–60 mg, lurasidone 80–120 mg, and placebo groups, respectively.
* p,0.05; ** p,0.01; *** p,0.001

Loebel A et al. Am J Psychiatry 2014;171:160

Lurasidone as Adjunctive Therapy for the Treatment of Bipolar I Depression







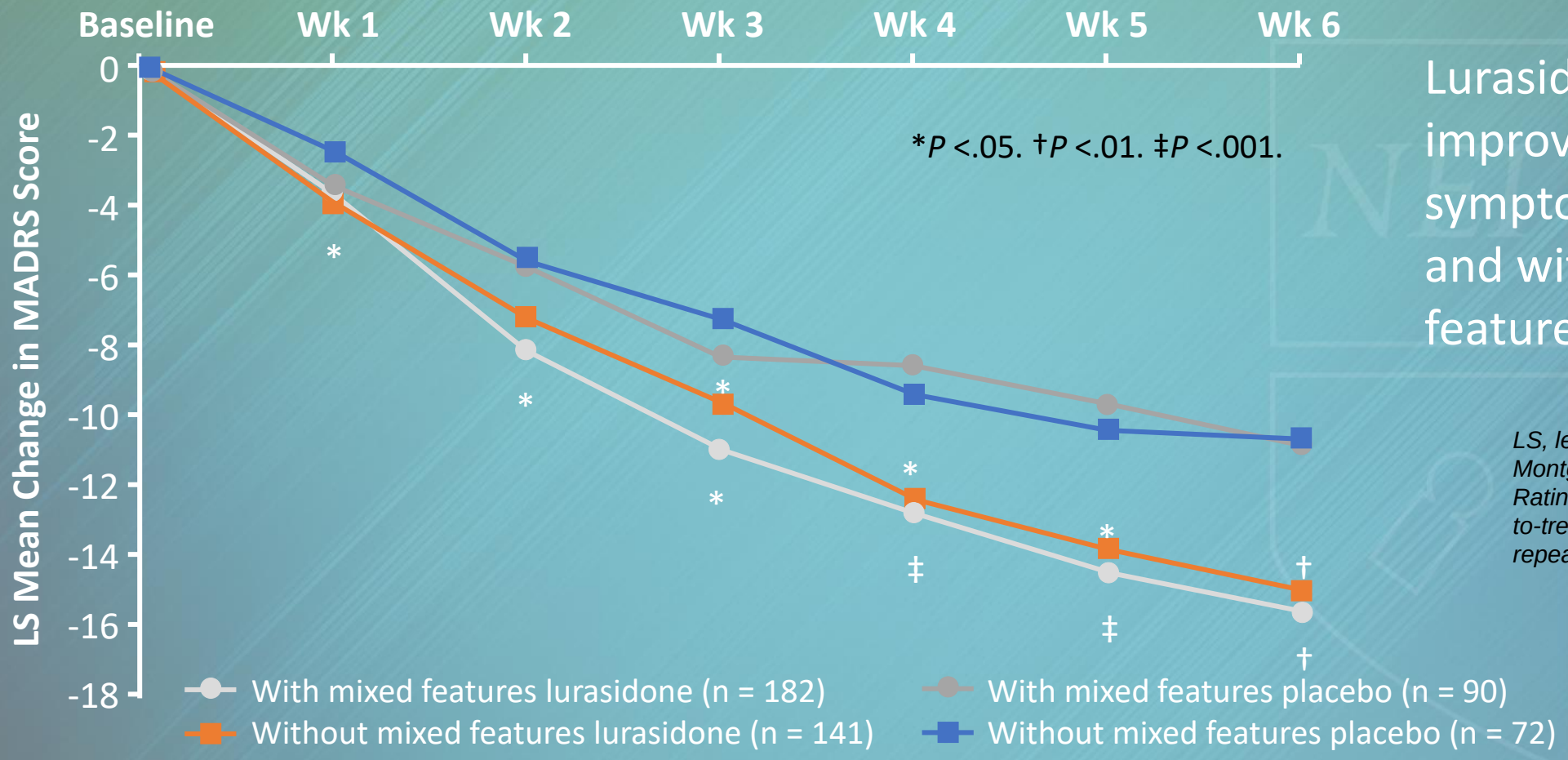
A randomized, double-blind, placebo-controlled study

A. Mean scores at baseline were 30.6 (SD=5.3) and 30.8 (SD=4.8) for the lurasidone and placebo groups, respectively.
B. Mean scores at baseline were 4.47 (SD=0.65) and 4.60 (SD=0.63) for the lurasidone and placebo groups, respectively.
* p,0.05; ** p,0.01; *** p,0.001

Loebel A et al. Am J Psychiatry 2014;171:169-77.

Bipolar Depression With Mixed Features: Lurasidone

Change From Baseline in MADRS Score (MMRM):
Patients With and Without Mixed Features at Baseline (mITT Population)

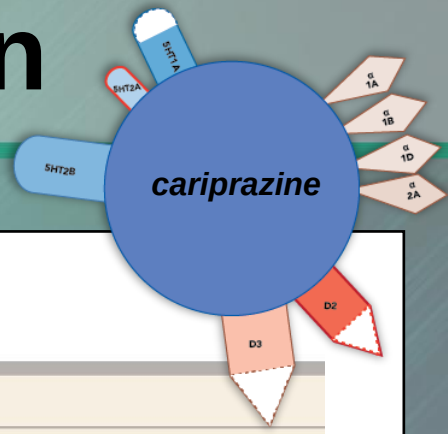


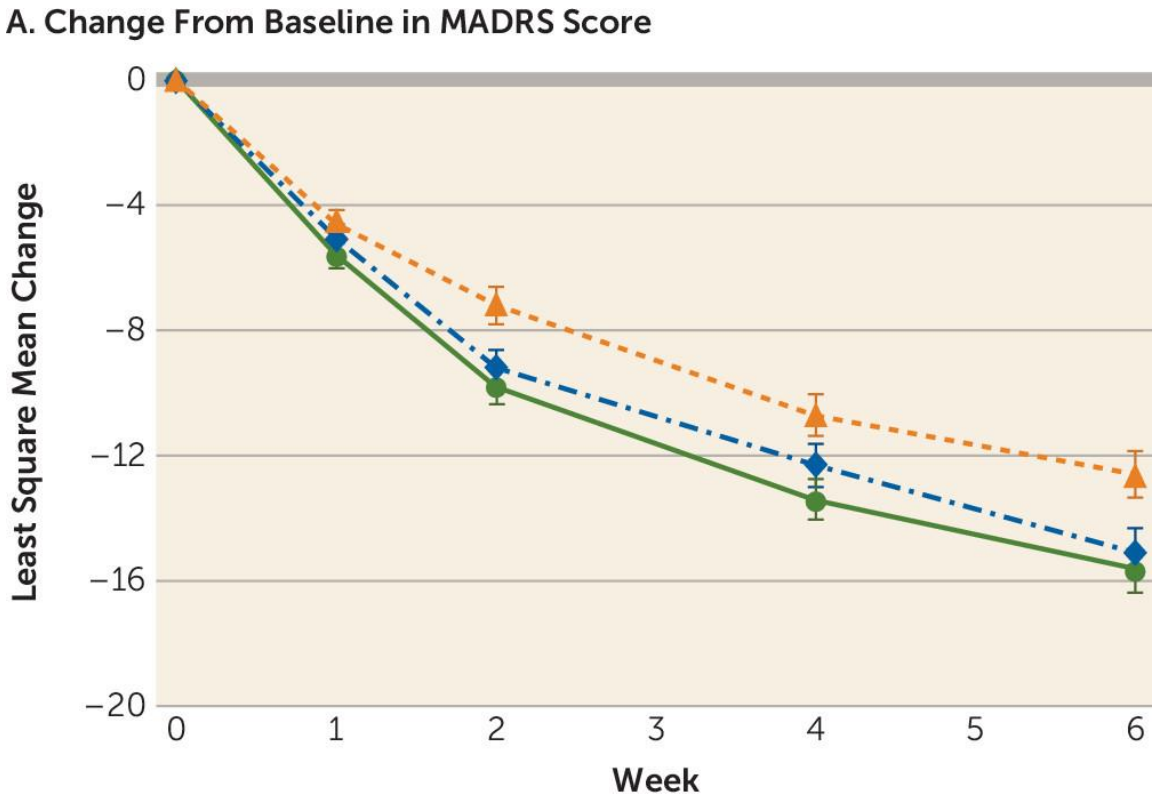
Lurasidone effective in improving depressive symptoms both with and without mixed features

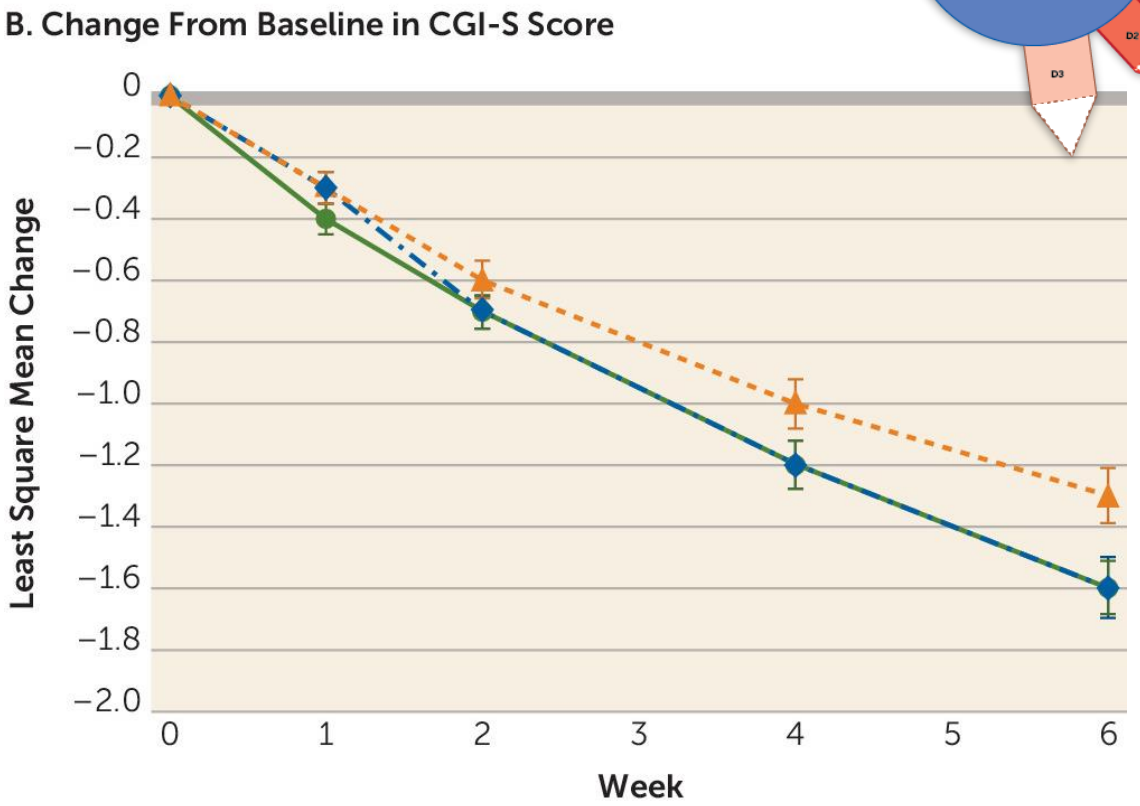
LS, least squares; MADRS, Montgomery-Asberg Depression Rating Scale; mITT, modified intention-to-treat; MMRM, mixed model for repeated measures.

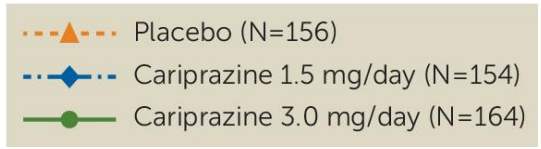
McIntyre et al. J Clin Psychiatry 2015;76(4):398-405.

Cariprazine for Bipolar Depression





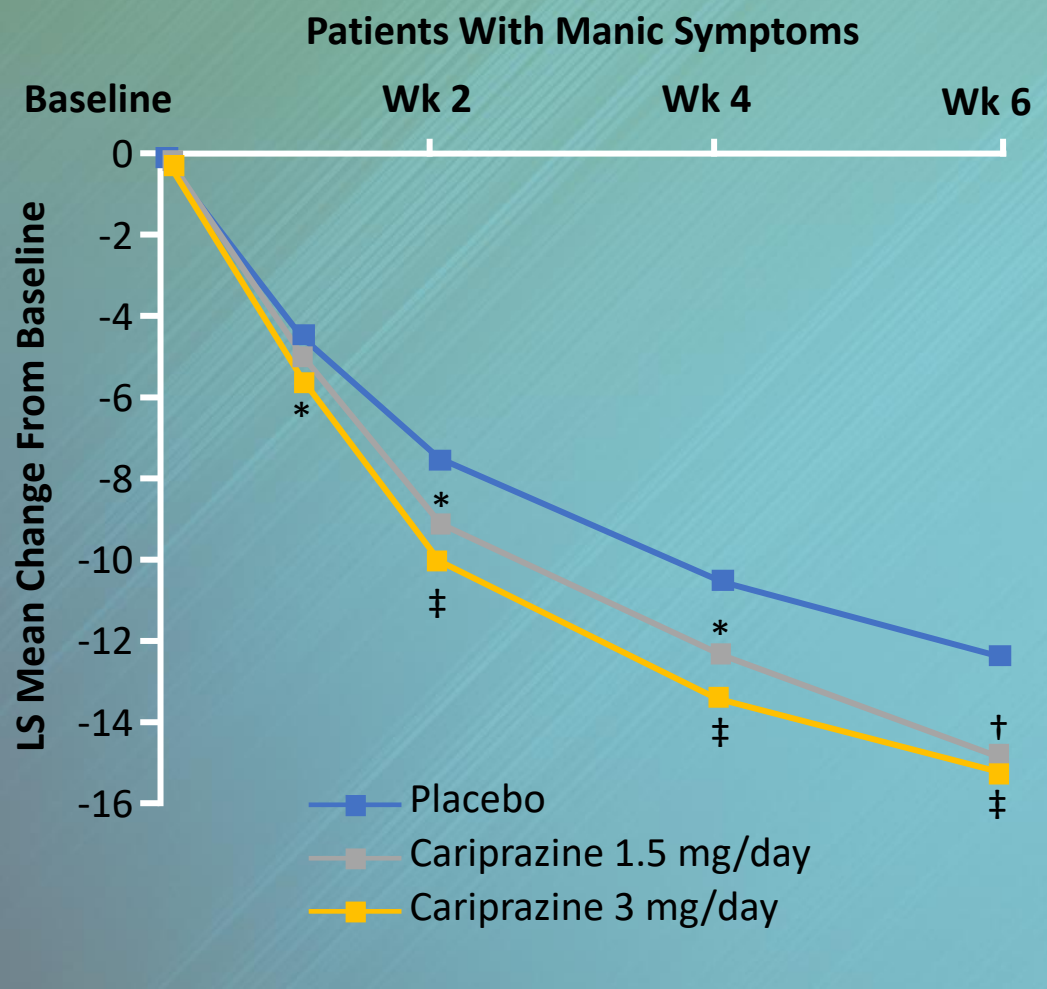


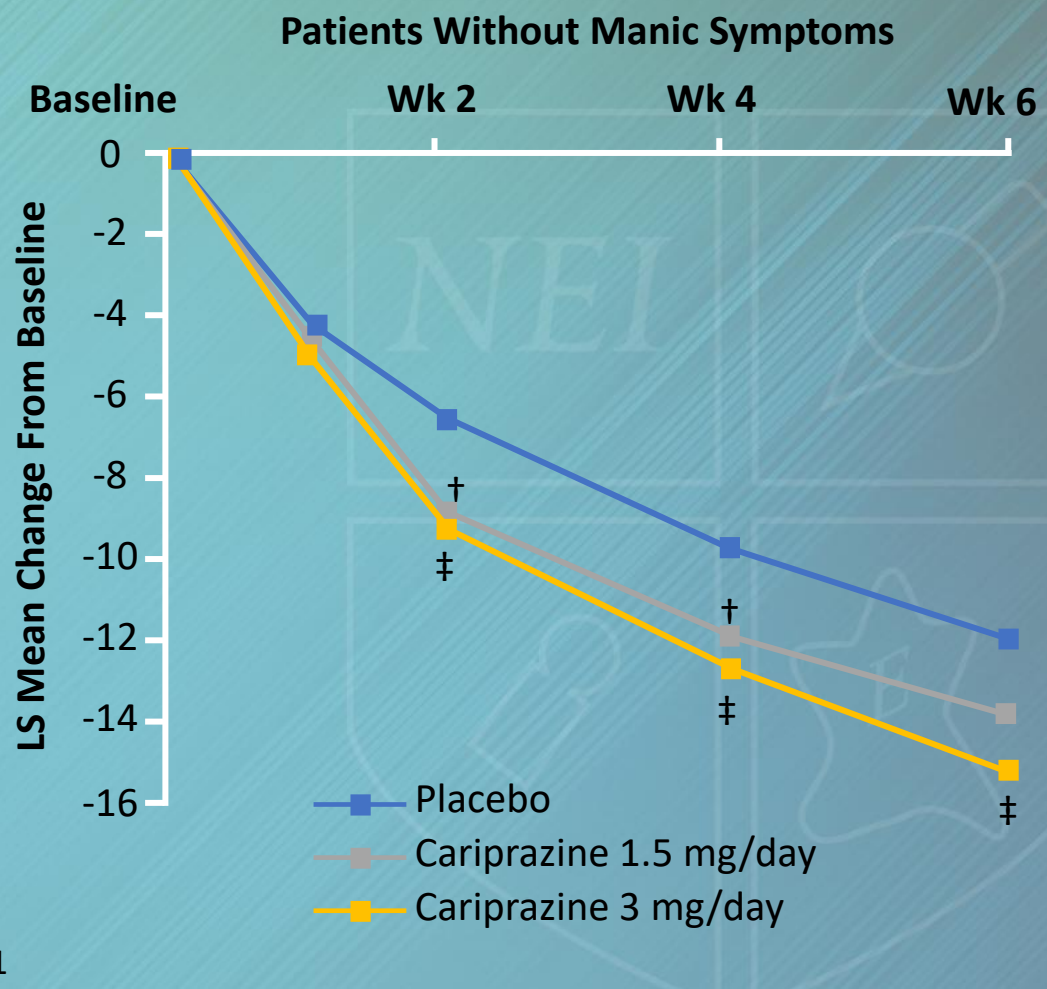


Earley W et al. Am J Psychiatry 2019;176(6):439-48.

Cariprazine in Bipolar Depression With or Without Manic Symptoms

Pooled Analysis of 3 Randomized Trials

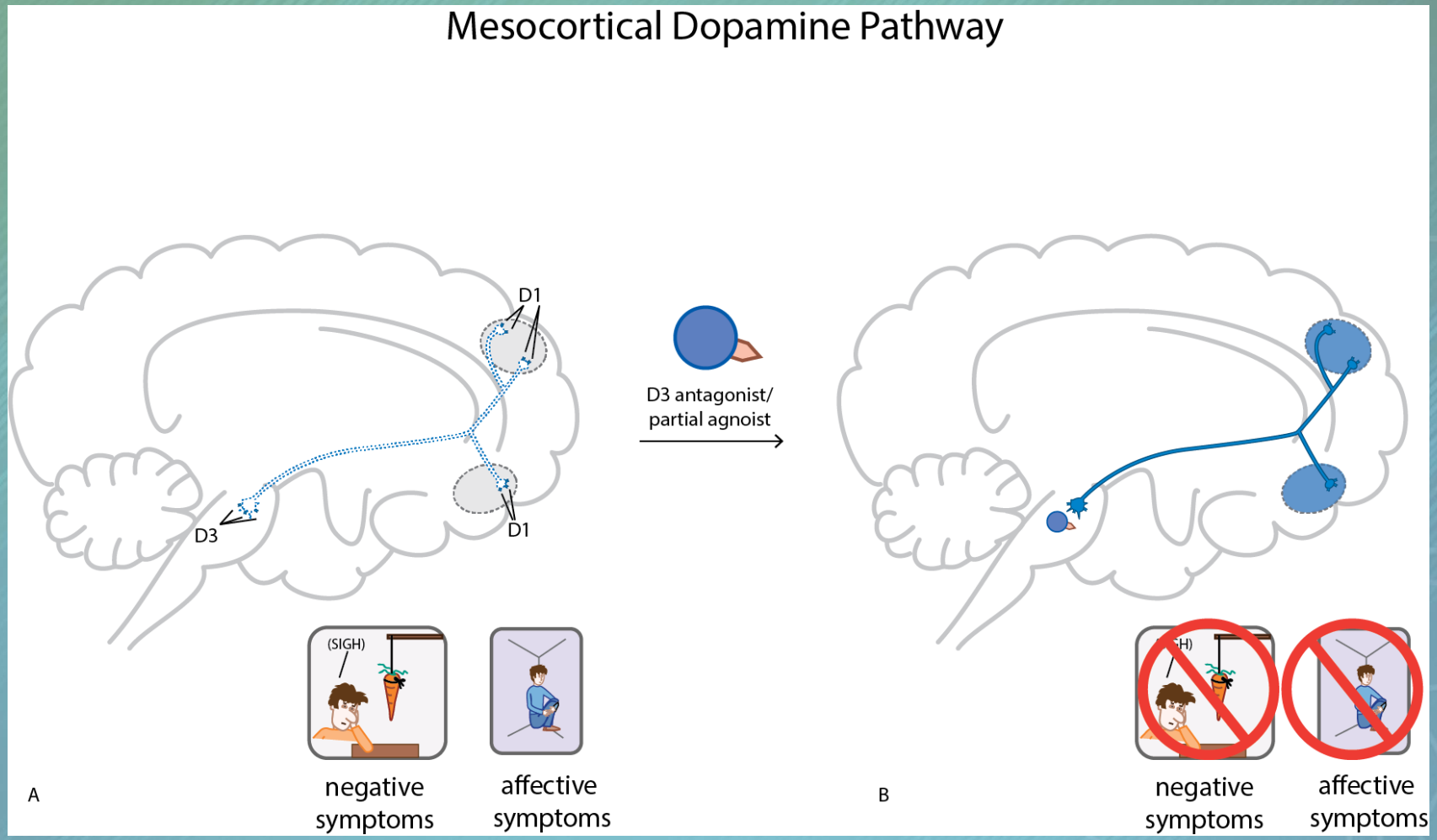




*P <.05
†P <.01
‡P ≤.001

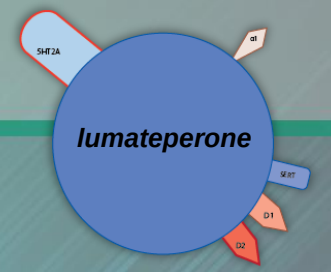
McIntyre et al. CNS Spectr 2020;25:502-10.

Cariprazine Mechanism of Action



Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

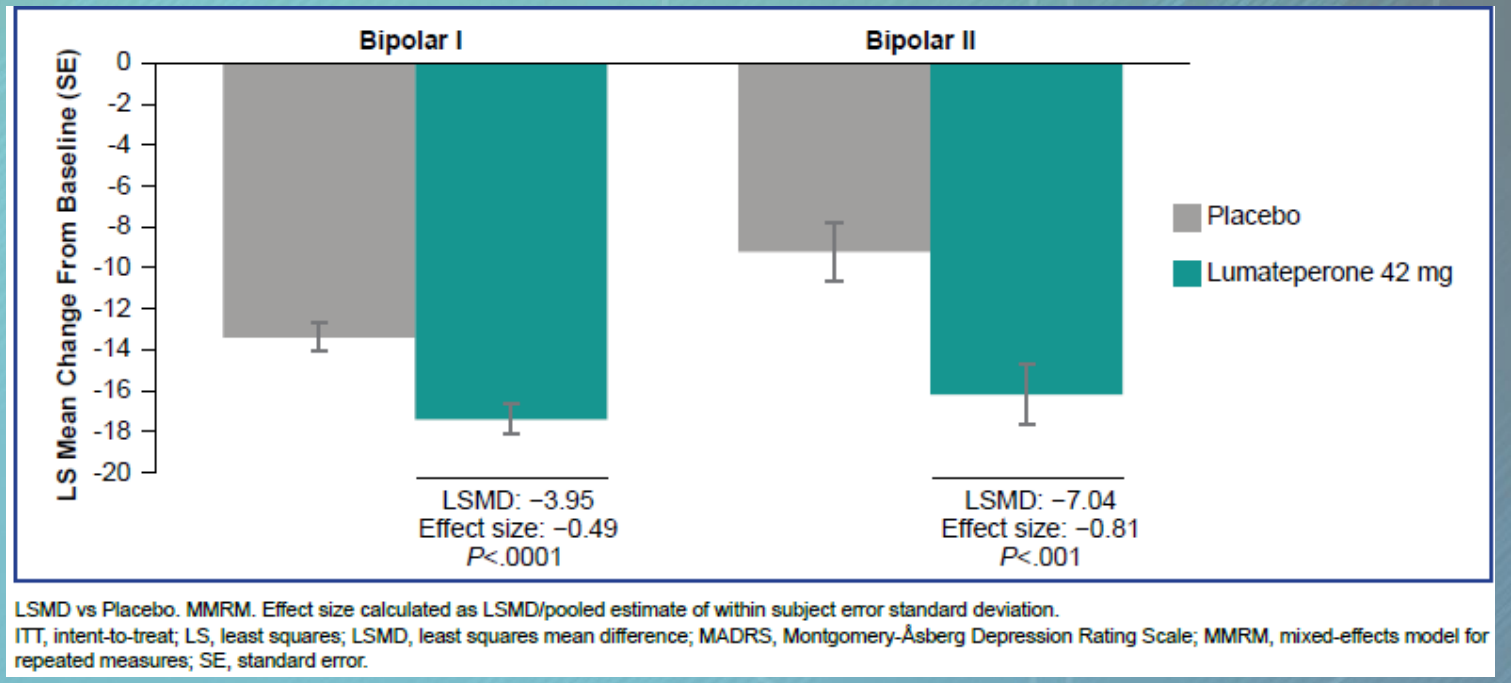
Lumateperone in Bipolar Depression



Received FDA approval for bipolar depression on Dec 20, 2021

Lumateperone 42mg vs. placebo once daily for 6 weeks

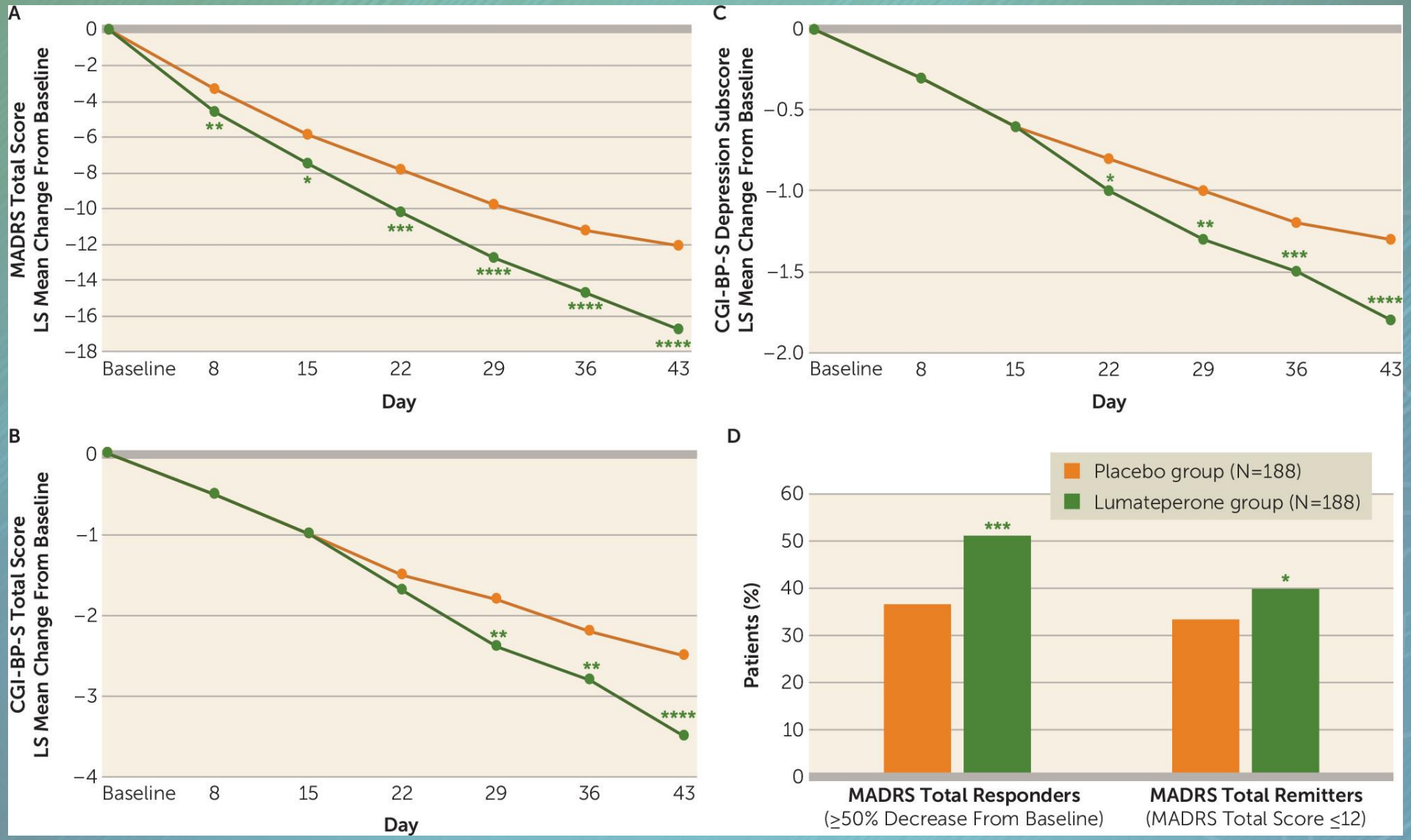
- Greater improvement from baseline on MADRS
- Greater improvement from baseline in CGI-Bipolar
- 51% responders (MADRS improvement ≥50%) vs. 37% for placebo
- 40% remission rate (MADRS total score ≤12) vs. 34% for placebo



LSMD vs Placebo. MMRM. Effect size calculated as LSMD/pooled estimate of within subject error standard deviation.
ITT, intent-to-treat; LS, least squares; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; SE, standard error.

Blair HA. Drugs 2020;80:417-23.

Lumateperone for MDE in BPI and BPII



Calabrese JR et al. Am J Psychiatry 2021;178(12):1098.

Safety Profile of Lumateperone in Bipolar Disorder

TABLE 3. Change in anthropometric and laboratory parameters at day 43 in a 6-week randomized controlled trial of lumateperone for major depressive episodes in bipolar I and II disorders (safety population)[a]

	Lumateperone Group (N=188)				Placebo Group (N=189)			
Measure	**Mean at Baseline**	**SD**	**Mean Change**	**SE**	**Mean at Baseline**	**SD**	**Mean Change**	**SE**
Weight (kg)	77.7	13.5	0.11	0.1	80.5	14.5	0.03	0.1
Body mass index	26.6	4.2	0.04	0.0	27.6	4.1	0.00	0.0
Waist circumference (cm)	90.5	13.2	−0.47	0.5	93.1	14.9	−0.08	0.2
Cholesterol (mg/dL)								
Total	187.9	41.0	3.7	3.1	195.4	47.9	−1.0	2.8
LDL	111.9	35.0	3.7	2.6	116.8	39.4	−1.1	2.4
HDL	49.7	13.8	0.2	0.8	49.7	13.6	−0.2	0.9
Triglycerides (mg/dL)	136.6	73.0	−5.7	5.3	143.6	98.8	−3.7	5.9
Glucose (mg/dL)	96.7	17.6	−0.5	1.2	95.7	12.7	1.0	1.3
Insulin (mIU/L)	14.51	14.5	−0.06	1.4	17.44	21.0	−0.1	1.9
Prolactin (µg/L)	13.7	13.7	−0.8	1.1	15.1	15.8	1.7	1.3

[a]HDL=high-density lipoprotein; LDL=low-density lipoprotein.

* The only extrapyramidal symptom-related treatment-emergent adverse event was one case (0.5%) of mild dyskinesia in the lumateperone group. This patient had a history of tardive dyskinesia.

Calabrese JR et al. Am J Psychiatry 2021;178(12):1098.

Lumateperone As Adjunctive Therapy to Lithium or Valproate

- Study 402 (6-week, Phase 3 Trial that included 529 patients with moderate to severe depressive episodes associated with bipolar I and bipolar II disorder)
- Randomized to 42mg of lumateperone, 28mg of lumateperone, or placebo in addition to lithium or valproate
- At week 6, once-daily 42mg of lumateperone met the primary endpoint for improvement in depressive symptoms (measured as change from baseline on the Montgomery-Asberg Depression Rating Scale)
- Statistically significant improvement on the Clinical Global Impression Scale for Bipolar for Severity of Illness-Depression subscale score was also observed with 42mg lumateperone
- Results suggest that lumateperone is effective for bipolar depression as monotherapy or adjunctive therapy

Intracellular Press Release: https://ir.intracellulartherapies.com/news-releases/news-release-details/intra-cellular-therapies-announces-positive-topline-results

Mood Stabilizers

	Evidence of efficacy in DMX	FDA-approved for BP depression	FDA-approved for BP mania	FDA-approved for BP maintenance	FDA-approved for MDD
Carbamazepine			☑		
Lamotrigine				☑	
Lithium			☑	☑	
Valproate			☑		

- No mood stabilizer is approved for use in depression of any kind (unipolar, mixed, bipolar)
- There are some data for the efficacy of lamotrigine or valproate for bipolar depression
- Lithium is well known for its anti-suicide effects; however, neither lithium nor carbamazepine monotherapy is recommended for the treatment of bipolar depression

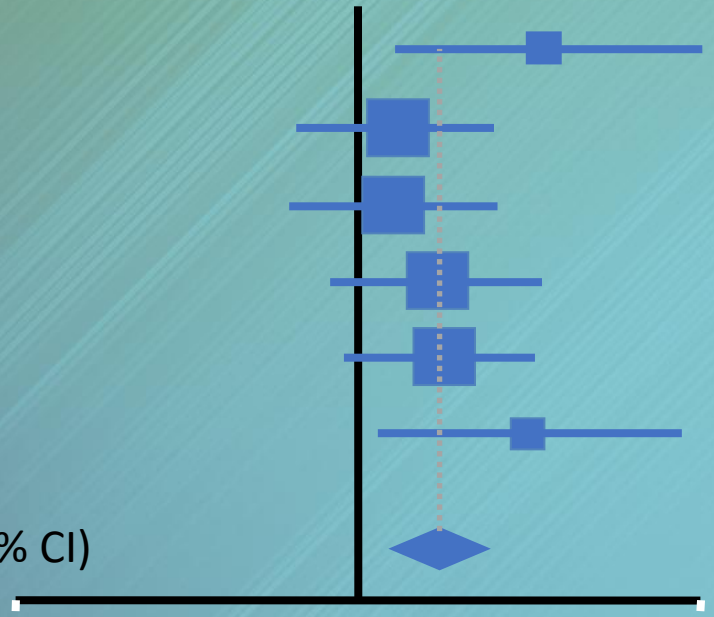
Stahl SM. Prescriber's guide. 6th ed. Cambridge University Press; 2018; Goodwin GM et al. J Psychopharmacol 2009;23(4):346-88; Connolly KR, Thase MD. Primary Care Companion CNS Disord 2011;13(4):PCC.10r01097; Musetti L et al. CNS Spectrums 2013;18(4):177-87.

Lithium

- Most effective drug for the treatment of recurrent depression and bipolar disorders
- Most stabilizing agent available
  - Little risk to worsen depression (like antipsychotics)
  - Little risk to worsen mania (like antidepressants)
- Anti-suicidal
  - Depression with mixed features is associated with high risk of suicidality
  - Lithium has been shown to prevent suicide, regardless of diagnosis
- May have side effects less dangerous than those associated with antipsychotics or other anticonvulsants
- Can be used in populations where mixed states are more prevalent
  - Pediatric (age 12+)
  - Postpartum
- Protective effect against neurodegenerative changes
- Randomized, controlled studies are lacking but observational studies support the use of lithium in mixed depression
- More clinical studies are needed

Kelly T. Bipolar Disord 2019;21(4):302-8; Manchia M et al. Bipolar Disord 2019;21(5):458-9; Sani G, Fiorillo A. CNS Spectr 2020;25(4):449-51.

Meta-Analysis of Lamotrigine in Acute Treatment of Bipolar Depression



Study	Risk Ratio (95% CI)	Weight, %
SCAB2001	1.71 (1.08–2.69)	8.3
SCAA2010	1.11 (0.83–1.48)	20.6
SCA40910	1.09 (0.81–1.48)	21.7
SCA30924	1.24 (0.91–1.70)	19.9
SCA10022	1.26 (0.95–1.67)	20.7
LAMLIT	1.63 (1.05–2.53)	8.8
Overall (95% CI)	1.26 (1.10–1.44)	

0.371223
Favors PBO

Risk Factors

2.6938
Favors drug

PBO, placebo.

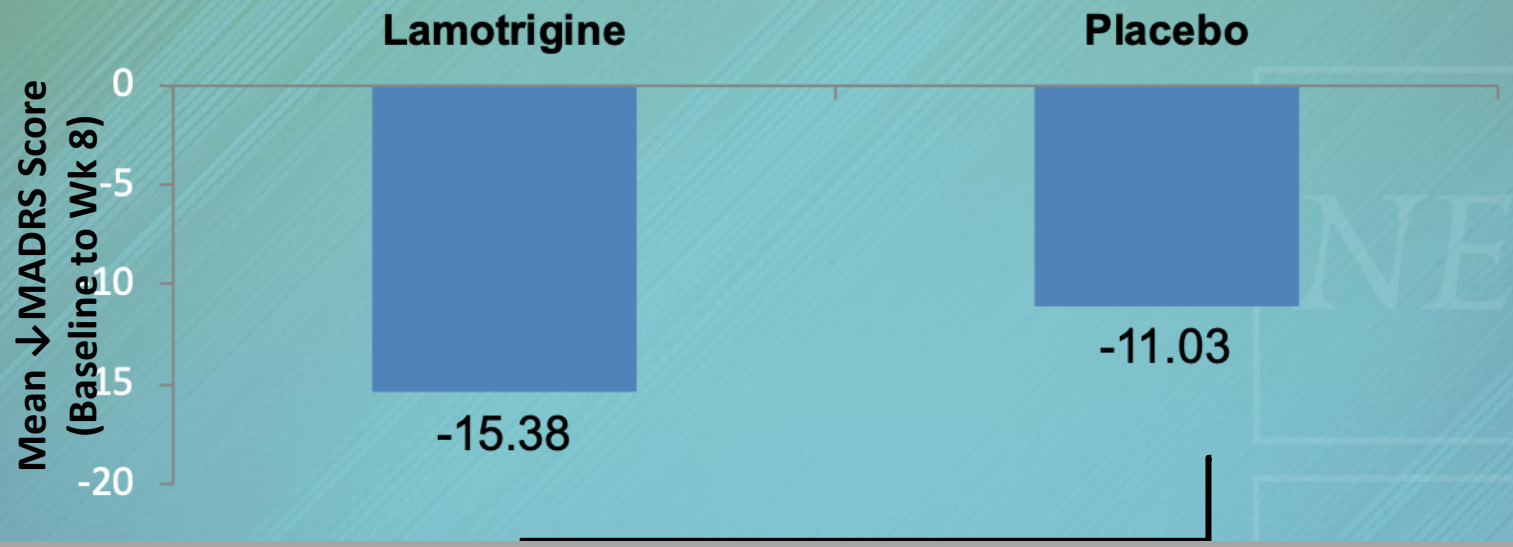
Lamotrigine: >50% reduction on the Montgomery-Asberg Depression Rating Scale (MADRS)

Lamotrigine shows some efficacy in bipolar depression.

Geddes JR, Calabrese JR, Goodwin GM. Br J Psychiatry 2009;194(1):4-9.
Van der Loos MLM. J Clin Psychiatry 2009;70(2):223-31.

Lamotrigine* as Add-On Treatment to Lithium in Bipolar Depression

*Not approved by the FDA.



P = .024

CGI-BP, Clinical Global Impressions scale, bipolar version; MADRS, Montgomery-Asberg Depression Rating Scale.

Endpoint, %	Lamotrigine	Placebo	*P*
≥50% ↓ MADRS	51.6	31.7	.03
CGI-BP change of depression ≤2	64.1	49.2	.105
Switch to mania/hypomania	7.8	3.3	.441
Response and no switch to mania/hypomania	60.9	46.7	.149

Van der Loos MLM. J Clin Psychiatry 2009;70(2):223-31.

FDA-Approved Treatments for Pediatric Bipolar Disorder

Acute Mania	Acute Bipolar Depression	Longer-Term
Year/ Drug	Year/ Drug	Year/ Drug
1970 Lithium **(Age ≥ 12–17)**	2014 Olanzapine+fluoxetine combination **(Age 10–17)**	1 Lithium **(Age ≥ 12–17)**
2007 Risperidone **(Age 10–17)**	**2018 Lurasidone(Age 10–17)**	2008 Aripiprazole **(Age 10–17, ->e)**
2008 Aripiprazole **(Age 10–17),(*->e)**		
2009 Quetiapine **(Age 10–17)**		
2009 Olanzapine **(Age 13–17)**		
2015 Asenapine **(Age 10–17)**		

Unmet Need

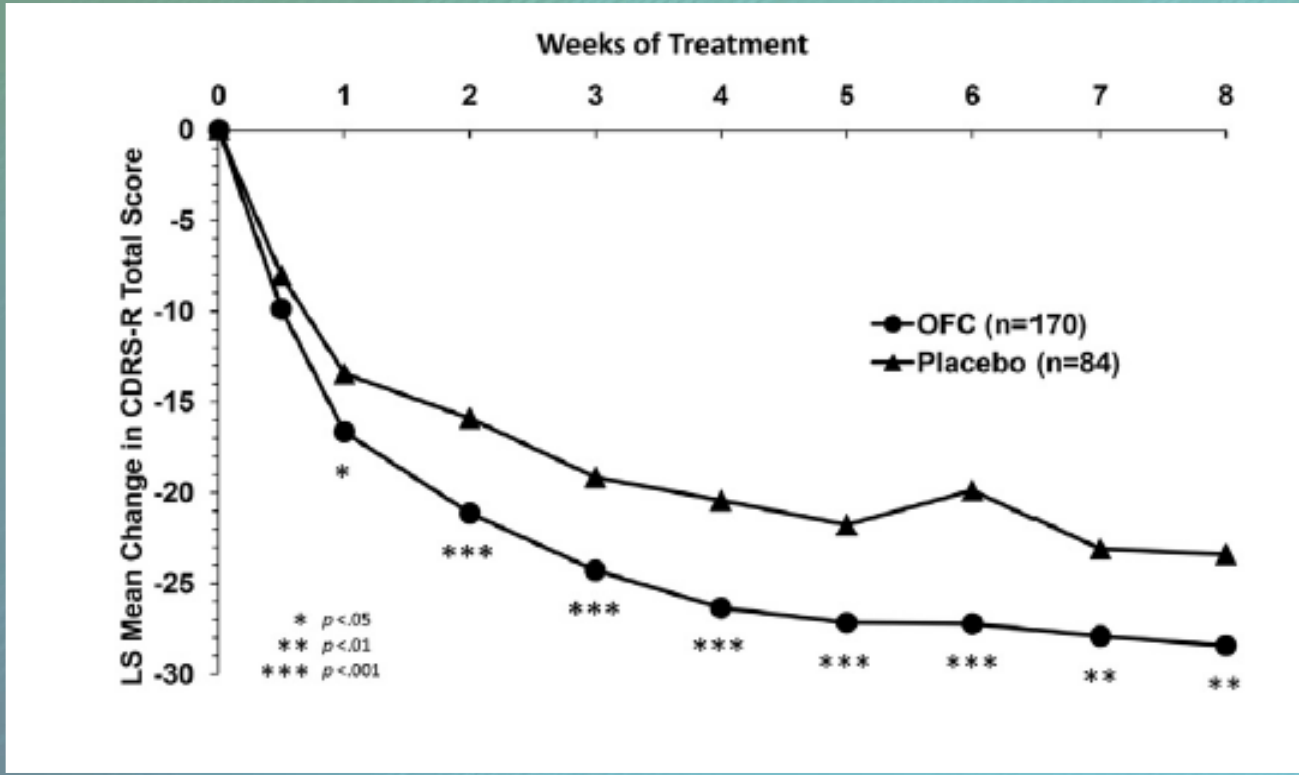
Unmet Need

***Adjunctive (as well as monotherapy);**
(->e)Extrapolated indication

Important unmet needs—well-tolerated treatments for acute depression and maintenance

Adapted from Ketter TA (ed). Advances in the treatment of bipolar disorder, Am Psych Pub, Inc., Washington, DC; 2015; Roley-Roberts ME, Fristad MA. J Clin Child Adolesc Psychol 2021;50(4):464-77.

Olanzapine/Fluoxetine Combination (OFC) in Children and Adolescents With Bipolar I Depression:



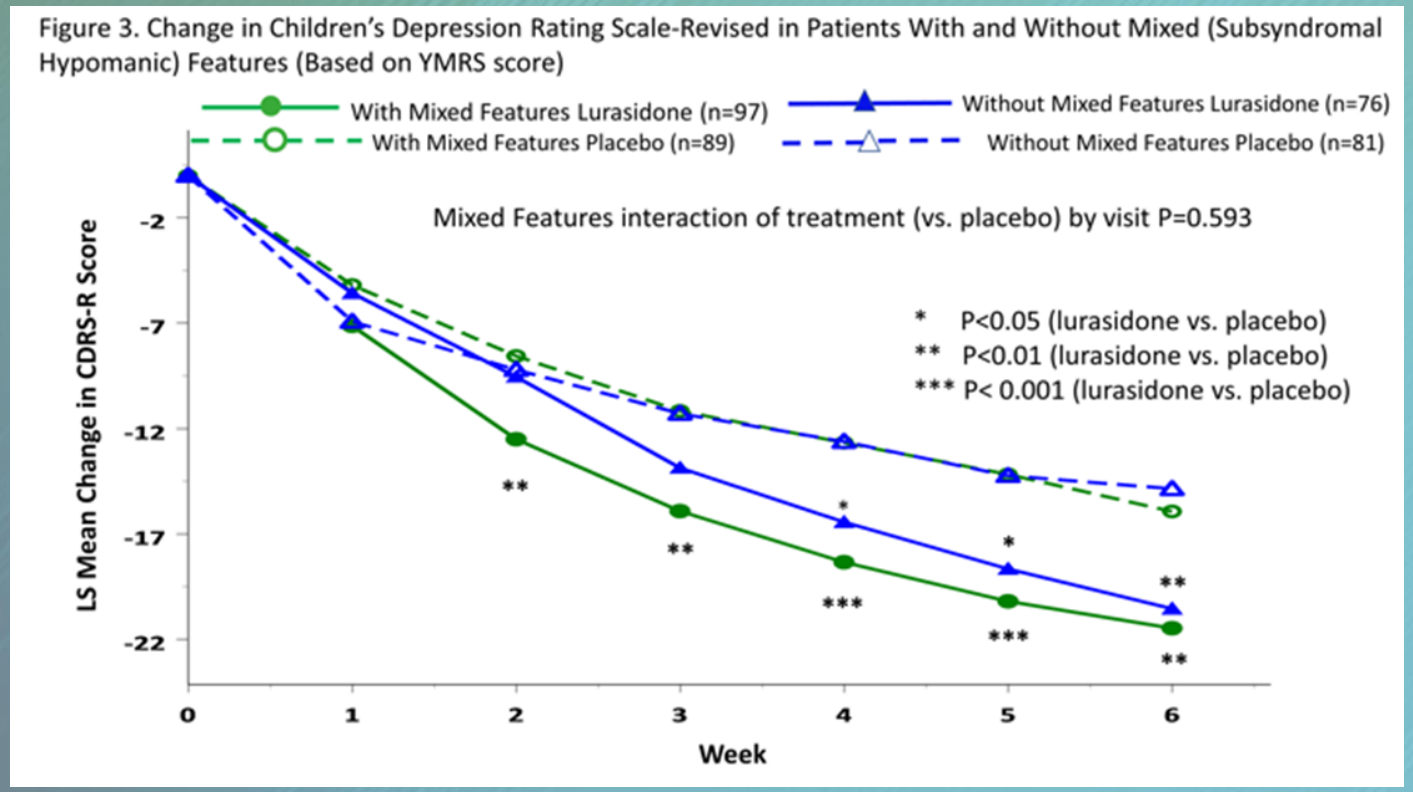
Rates of and times to response and remission were statistically significantly greater for OFC- than for placebo-treated patients.

Visitwise mean change in Children's Depression Rating Scale–Revised (CDRS-R) total score (mixed-model repeated measures). LS= least-squares; OFC=olanzapine/fluoxetine combination.

Detke HC et al. JAACAP 2015;54(3):217-24.

Lurasidone in Pediatrics With Mixed Features

Youth with Bipolar I Depression have similar efficacy/safety profiles with/without subsyndromal hypomania



Findings: lurasidone improved depressive symptoms in youth with and without mixed features compared to placebo.

Future Directions: Better understand the longer-term effects of treatment on complex symptoms, especially if they drive prognosis.

Singh et al. Journal of Child and Adolescent Psychiatry 2020;30(10):590-8.

Positive Studies for “Mood Stabilizers” in Pediatric BD

- **LITHIUM**: FDA-approved down to age 12 y/o; lithium superior to placebo in children with BD, little weight gain
- **LAMOTRIGINE**: Open studies find efficacy in pediatric acute mania, mixed mania, depression; **maintenance RCT study showed benefit as an adjunct**
- DIVALPROEX: Extended-release form was negative for acute mania; unpublished data suggests immediate-release more effective than placebo; inferior to quetiapine and risperidone
- CARBAMAZEPINE: ER form with open label data showing mild to moderate improvement in pediatric mania

PIPELINE

CARIPRAZINE: effective and well tolerated in youth down to age 6 in retrospective chart review; RCT results pending

Liu et HY al. J Am Acad Child Adolesc Psychiatry 2011;50(8):749-62; Findling RL et al. J Am Acad Child Adolesc Psychiatry 2015;54(12):1020-31; Findling RL et al. Pediatrics 2015;136(5):885-94; Findling RL et al. J Am Acad Child Adolesc Psychiatry 2019;58(2):287-96; Wagner KD et al. J Am Acad Child Adolesc Psychiatry 2009;48(5):519-32; Joshi G et al. J Child Adolesc Psychopharmacol 2010;20(1):7-14; Poweleit EA et al. J Child Adolesc Psychopharmacol 2020;30(4):267-72.

Network Meta-Analysis: Bipolar Depression in Youth

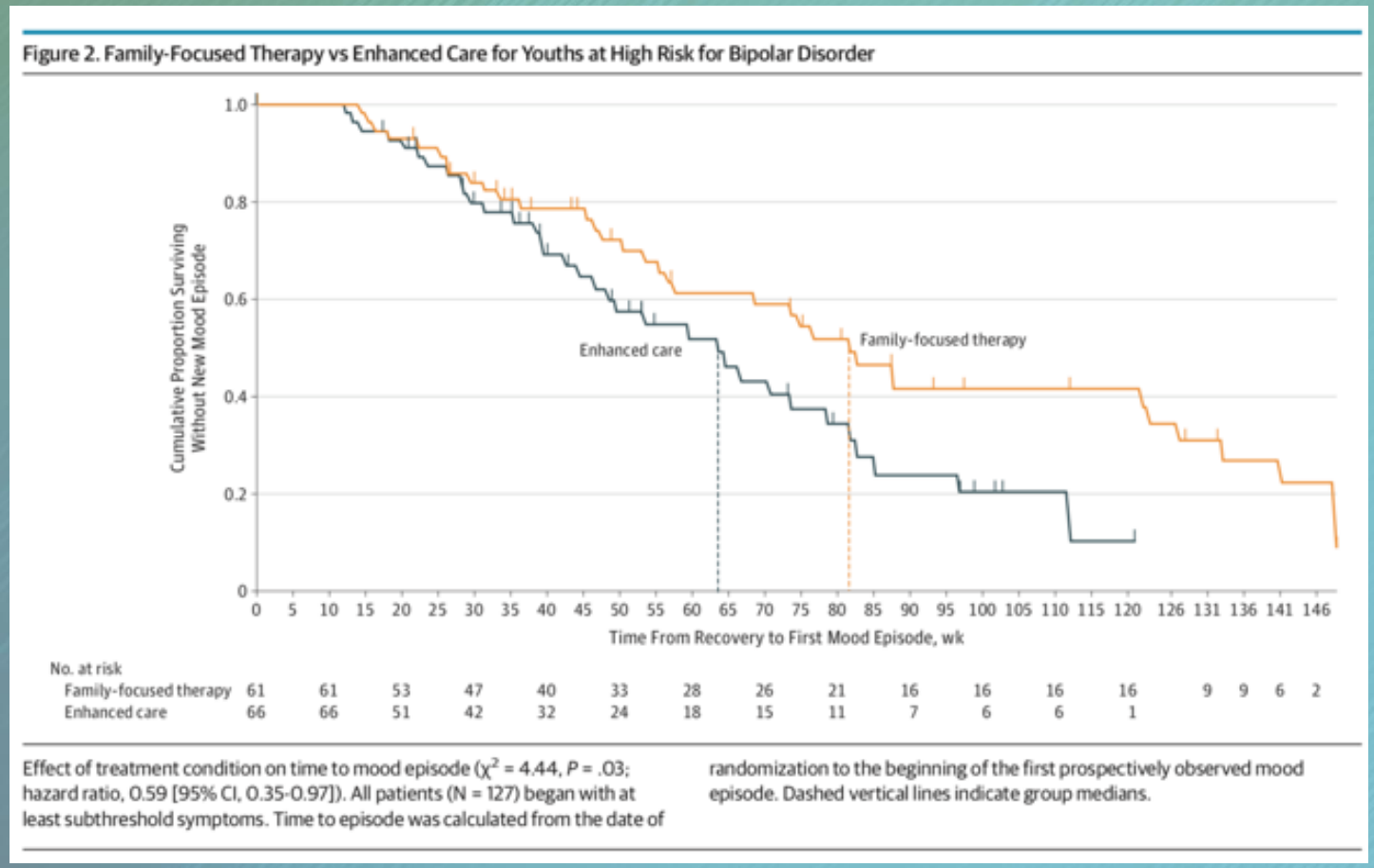
TABLE 2 Included Studies and Baseline Characteristics

Study	Duration	Comparison	n	Age y	Female patients %	Age at onset y	Weight kg	Bipolar I %	CDRS-R	CGI-BP-S depression	CGI-BP-S overall
DelBello 2017[28]	6 wk	Lurasidone 20–80 mg	175	14.2	49.1	12.4	56.6	100.0	59.2	4.6	4.5
		Placebo	172	14.3	48.8	12.2	57.0	100.0	58.6	4.5	4.4
DelBello 2009[26]	8 wk	Quetiapine 300–600 mg	17	16.0	71.0	12	NR	100.0	53.5	NR	5.4
		Placebo	15	15.0	67.0	11	NR	100.0	53.9	NR	5.5
Detke 2015[29]	8 wk	OFC (6/25–12/50 mg)	170	14.6	51.0	NR	NR	100.0	54.6	4.5	4.4
		Placebo	85	15.0	46.0	NR	NR	100.0	53.7	4.4	4.3
Findling 2014[25]	8 wk	Quetiapine XR 150–300 mg	93	13.9	51.1	NR	65.4	81.5	61.6	NR	NR
		Placebo	100	14.0	48.0	NR	63.6	79.0	60.1	NR	NR

Note: Values for baseline characteristics represent mean values for the study sample unless otherwise indicated. CDRS-R = Children's Depression Rating Scale–Revised; CGI-BP-S = Clinical Global Impression–Bipolar Severity; NR = not reported; OFC = olanzapine–fluoxetine combination.

DelBello MP et al. JAACAP 2022;61(2):243-54.

Prevention: Family-Focused Therapy (FFT) Delays New Mood Episodes by 20 More Weeks Than Enhanced Care (EC)

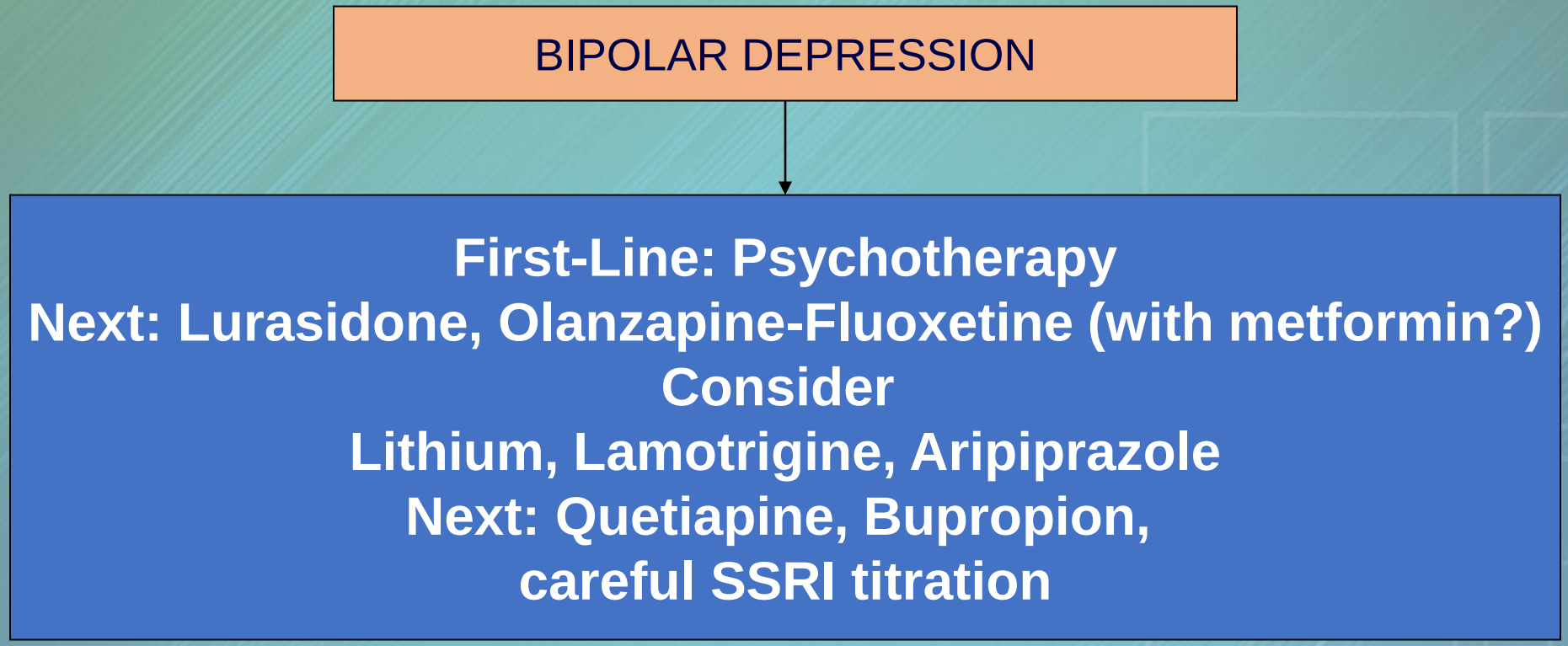


Finding: Family prosocial skills-training for youths at high risk for bipolar disorder is associated with longer intervals between depressive episodes.

Future Direction: Clarify the relation between changes in family function and changes in the course of high-risk syndromes.

Miklowitz DJ et al. JAMA Psychiatry 2020;77(5):455-63.

Possible Treatment Algorithm for Pediatric Bipolar Depression



Schneck CD et al. JCAP 2017;27(9):796-805; DelBello MP et al. JAACAP 2017;56(12):1015-25;
Findling RL et al. J Am Acad Child Adolesc Psychiatry 2015;54(12):1020-31.

Summary

- Up to 60% of patients with bipolar depression are misdiagnosed with unipolar depression
- There are many factors and challenges that contribute to misdiagnosis
- Being able to distinguish bipolar from unipolar depression with accurate screening for hypomania/mania will improve diagnoses
- There are several agents on-label and off-label that are effective in the treatment of bipolar depression across the lifespan

Posttest Question 1

According to research, which features are more common in bipolar depression than in unipolar depression?

1. Longer depressive episodes
2. Somatic complaints
3. Hypersomnia/increased daytime napping
4. Later age of onset (>25)
5. Weight loss

Posttest Question 2

In bipolar disorder, which mood state is most likely to present in the earlier part of the life cycle versus the later part?

1. Melancholia
2. Mixed
3. Mania
4. 1 and 2
5. 2 and 3

Posttest Question 3

Which of the following medications approved for bipolar depression in adults is also approved for bipolar depression in pediatrics?

1. Olanzapine-fluoxetine
2. Lumateperone
3. Lurasidone
4. Quetiapine
5. 1 and 3
6. 2 and 4